

ANNUAL REPORT
OF
PROGRAM ACTIVITIES
NATIONAL CANCER INSTITUTE
Fiscal Year 1981
Part IV-B

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service National Institutes of Health





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Division of Resources, Centers & Community Activities

RC
267
126
1981
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PROJECT SUMMARIES



Intraagency Agreement 00609: Demonstration Programs for Safe Asbestos Removal or Treatment in Schools

From 12/03/79 to 12/02/81

FY 81: 0 (Ann. \$450,000)

Roger A. Nelson, J.D., National Institute for Occupational Safety and Health,
5600 Fishers Lane, Rm. 8-63, Rockville, Maryland 20857

Objectives: To develop demonstration programs for the dissemination of information about accepted methods for safe removal, encapsulation, or enclosure of deteriorated asbestos previously used in the construction of schools. Such procedures include the proper worksite isolation, ventilation, use of respirators and protective clothing, and safe disposal of the asbestos which has been removed. OSHA regulations governing workplace exposure to asbestos are to be followed.

Target audiences include state and local school and health officials, contractors and their employees and school maintenance personnel. Information to be disseminated about accepted procedures would be similar to that presented in EPA guidelines and NIOSH manuals.

Accomplishments: Seven demonstration grants were awarded under this program.

The accomplishments, covering the period of June 1, 1980, to December 1, 1980, are as follows:

Project staff of the Colorado State University have identified school districts, personnel, and facilities within Colorado, and such information has been stratified for random sampling and initiation of program field activities. Contacts have been made with key education officials, the Associated General Contractors of Colorado, and the AFL-CIO Building and Construction Trades personnel relative to training activities and appropriate training modes.

Six regional asbestos workshops have been presented in Oklahoma by the State Department of Education, the State Health Department and EPA. The major thrusts of the workshops were to present the current proposed regulations from EPA, a review of the current OSHA regulations, and a detailed discussion of the corrective action alternatives. In addition, various materials were reproduced for the workshops. These materials covered such subjects as available disposal sites, asbestos contractors, resource personnel and government publications.

Work has begun at the Wisconsin Department of Health and Social Services on the computerization of data collected prior to the grant award. A follow-up program has been instituted to monitor the effectiveness of corrective actions taken by schools. Educational materials directed at contractors, architects, engineers, and school building officials are being developed. This project constitutes a model statewide surveillance system, and contains a follow-up evaluation of recommendations concerning the removal of asbestos from individual schools.

In Missouri, University of Missouri personnel have made an extensive review of audiovisual materials. Some lesson plans have been completed and the remainder are being prepared. Plans are progressing for the first workshop which will be held shortly. One day seminars will be conducted at four Missouri locations:

Project Officer: Margaret H. Sloan, M.D.

Columbia, Rolla, St. Louis and Kansas City. The first workshop will be a prototype production at Columbia and will be open to school administrators, contractors, and workers. Later, workshops at the same location will be open to similar groups both in and out of state.

In Illinois, the Winnebago County Health Department has hired a health educator and an interdisciplinary panel has been selected. A lecture series and educational materials targeted at key groups which have decision making, monitoring, enforcement, maintenance or active corrective type roles in schools and other structures which might contain asbestos are being developed. Ongoing reinforcement during the course of the project is the responsibility of a specifically trained local interdisciplinary panel.

The Hawaii Department of Health has begun the first of three phases of its demonstration program. Sessions have been scheduled to provide workshop training of State and local officials and contractors in proper, accepted procedures for safe removal, encapsulation and enclosure of asbestos materials.

In New Jersey, the Department of Environmental Protection has been involved in the location and identification of schools meeting the criteria for unsafe asbestos content and friability.

Plans: The scheduled expiration date of these grants is May 31, 1981. Due to scheduling, the bulk of the activities will be undertaken in the last half of the grant period. It is not expected at present that this program will be continued.

Publications: Author: Martin, Bob: Asbestos Abatement in Oklahoma Schools, Oklahoma State Department of Education, Oklahoma City, Oklahoma, 1980, 22 pp.

Interagency Agreement 00610: Revision, Reproduction, and Distribution
of Asbestos Removal or Treatment Audiovisual Materials

From 08/01/80 to 09/30/81

FY 81: 0 (Ann. \$100,000)

Mr. William C. Cain, Research Program Manager, Alternate Energy Sources Branch,
Environmental Protection Agency, 26 W. Saint Clair Street, Cincinnati, OH 45268

Objectives: To support (1) the incorporation of needed changes in audiovisual materials on safe methods of asbestos containment in schools, and (2) the production of 100 sets of those materials for distribution through the ten regional offices of the Environmental Protection Agency.

Accomplishments: The audiovisual materials, a set of which consists of a 20-minute film, four slide-tape presentations and accompanying illustrated brochures, were revised. Production of additional sets was delayed pending the necessary clearance from OSHA. This has now been obtained.

Plans: One hundred sets of the audiovisual materials will be distributed to the ten regional offices of EPA for loan to state and local departments of health and education and to contractors bidding on school asbestos removal or containment projects.

Project officer: Margaret H. Sloan, M.D.

Interagency Agreement Y01-CN-00711: Long-Term Mental Health Effects
of Prenatal DES Exposure

From 08/31/80 to 08/31/83 FY 81: \$107,000
Dr. Anke A. Ehrhardt and Dr. Heino F.L. Meyer-Bahlburg, New York State
Psychiatric Institute, 722 West 168th Street, New York, New York 10032

Objectives: Individuals who were exposed in utero to the synthetic estrogen diethylstilbestrol (DES), are at increased risk of developing a variety of genito-urinary abnormalities and cancer. Therefore, psychosocial and emotional sequelae of varying severity and duration of being identified as a DES daughter or DES son have been reported. Moreover, animal research strongly suggests lasting effects of DES on the developing brain and psychosexual development.

This study has three goals: (1) to assess psychosexual development of females and males aged 17-30 years who have been exposed in utero to DES; (2) to assess the impact of the disclosure of DES exposure and its health implications on psychosocial and emotional functioning of DES daughters and DES sons; (3) to construct a clinical manual for the psychosocial management of the ensuing problems of fetal DES exposure.

Plans: The investigators' aim is to conduct a psychological study of DES daughters (N=100) and their mothers; of a control group of women with abnormal Pap smear findings (N=100), pair-matched for age, race, and socioeconomic level; and of DES-unexposed female siblings of DES daughters (approx. N=50). They will also study DES sons (N=100) and their mothers, pair-matched control males with minor urologic abnormalities (N=100) and the unexposed male siblings of DES sons (approx. N=50). The psychological evaluation will focus on (1) psychosexual development (sex-dimorphic behavior, sexual activity) and (2) psychosocial and emotional factors (including psychiatric symptoms and diagnoses). Assessment methods will primarily rely on interviews and questionnaires and will be partly blind as to sample membership of the subject. Subjects' mothers will serve as informants on the study subjects and will, themselves, undergo a brief evaluation.

Accomplishments:

Method development and training of staff:

During the first three months, a team of excellent interviewers and researchers were hired and trained in the methodology of the project. The battery of tests, questionnaires and interviews specific to the DES population was finalized.

The staff was prepared and trained for the methodology of documenting DES exposure on the basis of medical charts for both DES females and DES sons. At the present time, staff members are working on a regular basis in both Dr. Norma Veridiano's office (DES Screening Center for females) and Dr. Douglas Whitehead's office (urology consultant for males).

Program Director: Sandra M. Levy, Ph.D.

Sample recruitment and data collection

The response of subject recruitment has been excellent. So far, we have not had one refusal. We anticipate seeing the following numbers of subjects of the various groups by September 30, 1981:

DES females:	N=40	DES sons:	N=30
Mothers of DES		Mothers of	
Daughters:	N=40	DES Sons.....	N=30
Controls:	N=20	Controls:	N=10
Mothers of Controls	N=20	Mothers of Controls	N=10
Unaffected Sisters:	N=20	Unaffected Brothers...	N=10

Contract 05458: Training Program for Maxillofacial Prosthodontists and
Maxillofacial Dental Technicians

From 10/1/80 to 06/29/82

FY 81: 0 (Ann. \$240,000)

Dr. Varoujan A. Chalian, Indiana University, School of Dentistry, 1121 West
Michigan Street, Indianapolis, Indiana 46202

Objectives: A training project designed to train prosthodontists clinically to treat head and neck cancer patients for their continuous comfort, functions and improved esthetics. Clinical training will be supported by seminars, lectures, clinical conferences and technic projects. Trainees will participate in multidisciplinary approach in the treatment of head and neck cancer. Prosthodontists and dental technicians will be exposed to different materials and technics used in maxillofacial prosthetics. Project necessary to fulfill the need for trained personnel in maxillofacial prosthetics.

Accomplishments: From October 1980 to March 1981.

I. Maxillofacial Prosthodontic Trainees:

A. Clinical: A total of 97 new patients were examined for Maxillofacial Prosthodontic Rehabilitation. A total of 571 patient visits were made in the Maxillofacial Prosthodontic Department. Approximately 35 patients had maxillary resection and 30 patients had mandibular resection. A total of 87 patients were treated for follow-up; 33 extra-oral prostheses and 44 intra-oral prostheses were delivered to the patients. About 87 patients were screened for detection of oral cancer. On 6 occasions prosthodontic residents assisted surgeons in operating room. A total of 15 patients were treated for radiation prostheses and oral management of chemotherapy.

II. Maxillofacial Dental Technicians:

Dental technician trainees made 137 study models, relined 30 ocular prostheses, and fabricated 27 different types of obturators. They made 79 upper and lower complete and partial dentures, 6 implants (cranial, mandibular, and melar). They fabricated 28 splints and stents, 8 radiation treatment prostheses and 7 unusual prostheses (anal, mouth stick, and finger).

III. Laboratory Technics:

Prosthodontic trainees and dental technician trainees made 12 and 9 technic projects respectively.

IV. Didactics:

A total of 4 review assignments were completed by each trainee. Lectures on maxillofacial prosthetics were scheduled every Tuesday and by now all major topics in maxillofacial prosthetics are covered.

About 24 seminars on maxillofacial prosthetics were presented every Friday and about 17 completed cases were presented every Thursday by prosthodontic and dental technician trainees.

Project Officer: Lawrence D. Burke

From April 1981 to September 1981, we hope to see approximately the same number of patients treated by our trainees during October 1980 to March 1981. Two prosthodontic trainees and two dental technician trainees have been selected for one year training in maxillofacial prosthetics for the year 1981-82.

Plans: Two prosthodontic and two dental technicians will complete their training in Maxillofacial Prosthetics by June 30, 1981. We plan to allocate more patients and expose our trainees to additional problem cases. We hope to finish our lectures, seminars and case presentations by June 30, 1981. We are planning to schedule an Oral Test in May 1981, to study effectiveness of our training.

Long-Term Follow-Up of the Breast Cancer Screening Project Participants

From 01/80 to 02/86

FY 81: \$2,824,147 (Ann. \$3,274,000)

Objectives: Original plans for the Breast Cancer Detection Demonstration Project (BCDDP) included screening 280,152 women for five annual examinations and then follow-up of the group for five additional years. During 1977, the plan for the follow-up phase was evaluated by the Working Group to review the BCDDP and in 1978 by the Project Coordination Working Group. Based on the identified lack of a non-screened comparison group and the self-selected nature and size of the BCDDP population which prohibited a complete evaluation of efficacy of screening or the hazards of radiation, follow-up of the total cohort was determined to be of little value and was not recommended. However, an appropriate sample from the total group followed for five and possibly ten years should allow major issues in detection, program evaluation, etiology, and natural history to be evaluated adequately. A carefully designed epidemiologic follow-up study involving approximately 65,000 women has been initiated to investigate a broad range of important scientific issues. The population of approximately 280,000 women intensively screened over a five year period, provides a unique base from which groups can be selected to study these issues. The Follow-Up Study will be carefully evaluated in its fourth year to determine if an additional five years are required. This long-term follow-up provides the opportunity to test hypotheses in detection, etiology, and natural history of breast disease. Carefully designed epidemiologic follow-up studies on the risks associated with mammographic or thermographic patterns or pathology subtypes can be carried out.

Although efficacy cannot be established, follow-up provides the opportunity to evaluate the impact of the screening programs on both the screenee and the health care delivery system with special consideration given to the established goals of the BCDDP.

<u>Contract #</u>	<u>Start</u>	<u>End</u>	<u>FY 81</u>	<u>Annual</u>	<u>PI/Organization</u>
05498	1/80	1/85	\$64,000	\$75,000	Philip Strax, M.D. Guttman Institute
05510	4/80	4/85	\$92,016	\$90,000	Hamblin Letton, M.D. Georgia Baptist Hospital
05502	2/80	2/85	\$44,722	\$48,000	Robert Egan, M.D. Emory University
05500	2/80	2/85	\$83,286	\$92,000	Jerry Buchanan, M.D. University of Louisville

Project Officer: Richard D. Costlow, Ph.D.

05492	3/80	3/85	\$82,087	\$91,000	John Milbrath, M.D. University of Wisconsin
05496	1/80	1/85	\$99,820	\$133,000	Thomas Carlile, M.D. Virginia Mason Institute
05494	2/80	2/85	\$119,666	\$131,000	JoAnn Haberman, M.D. Universisy of Oklahoma
05497	11/80	1/85	\$79,000	\$99,000	Elisabeth Ward, M.D. Mountain States Tumor Institute
05511	5/80	5/85	\$115,633	\$135,000	Benjamin Rush, M.D. College of Medicine & Dentistry of New Jersey
05495	2/80	2/85	\$75,893	\$78,000	Larry Baker, M.D. University of Kansas
05499	4/80	4/85	\$198,706	\$276,000	Myron Moskowitz, M.D. University of Cincinnati
05512	5/80	5/85	\$75,881	\$88,000	Leslie Whitney, M.D. Wilmington Medical Center
05514	6/80	6/85	\$177,725	\$195,000	Fred I. Gilbert, M.D. Pacific Health Research Institute
05517	7/80	7/85	\$83,520	\$92,000	Marvin McCloy, M.D. St. Vincent's Medical Center
05516	7/80	6/85	\$86,133	\$98,000	Harold Isard, M.D. Albert Einstein Medical Center
15539	2/81	2/86	\$95,216	\$109,000	Bernard Fisher, M.D. University of Pittsburgh
15540	2/81	2/86	\$162,975	\$182,000	Barbara Threatt, M.D. University of Michigan
15542	2/81	3/86	\$86,698	\$99,000	Donald Young, M.D. Iowa Lutheran Hospital

05519	9/80	9/85	\$102,384	\$112,000	Robert Schweitzer, M.D. Samuel Merritt Hospital
05518	2/81	3/86	\$112,666	\$125,000	William Feller, M.D. Georgetown University
15532	12/80	11/85	\$91,098	\$109,000	Diane McGrath, Ph.D. Duke University
15545	1/81	1/81	\$128,217	\$155,000	Arthur Present, M.D. University of Arizona
15541	2/81	1/86	\$140,919	\$158,000	Yeu-Tsu Lee, M.D. University of California, Los Angeles
15536	3/81	2/86	\$103,998	\$120,000	Ned Rhodes, M.D. Cancer Research Center
15537	2/81	1/86	\$83,526	\$97,000	Morton Goodman, M.D. Good Samaritan Hospital
15535	1/81	1/86	\$53,312	\$65,000	Herbert Constantine, M.D. Rhode Island Hospital
15544	2/81	2/86	\$80,033	\$92,000	Dee Ingram, M.D. Vanderbilt University
15538	3/81	2/86	\$105,017	\$130,000	John Martin, M.D. St. Joseph's Hospital

Accomplishments: The Long-Term Follow-Up Study will be performed by Projects' staffs from 28 of the screening centers that participated in the BCDDP. The follow-up was initiated with new contracts at the time each screening center terminated its contract for active screening. The contracts were initiated over a 14 month period from January 1, 1980 through March 1, 1981. To date, all 28 projects have begun follow-up activity beginning with verification of assigned cohorts. Following cohort verification, interview contacts have or will be initiated according to a Manual of Procedures and Operations which forms the standard protocol for all Projects to follow.

The latest report from the Data Management and Analysis Center, dated 05/06/81, listed the cohort at 64,115 participants. Of the 30,791 form sets submitted between 5/80 and 4/81 by 22 of the projects, 28,863 (94%) were completed interviews and 1,928 reported women lost to interview. Of the 1,928, 200 (10%) were delayed for more than 90 days, 841 (44%) refused to respond, 216 (11%) were unable to be located, and 671 (35%) were deaths.

Plans: The Project will be continued as planned.

From 2/1/80 to 1/31/83

FY 81: 0 (Ann. \$267,520)

Peter Wootton, University of Washington, RC-08, Seattle, Washington, 98195

Objectives: (1) to ensure uniform high quality radiological physics practices at DRCCA supported clinical facilities which use radiation for treatment or diagnosis of cancer, (2) to establish uniformity in dose specification in radiation treatments, (3) to reduce patient dose during diagnostic examinations (mammography, computerized tomography) by improving image quality, (4) to facilitate cancer control through technology transfer in the field of medical physics, (5) to serve as an educational and consultative resource in the region, (6) to provide other physics services as requested by the Project Officer, and (7) to collaborate with other CRP's and the Coordination Program.

Accomplishments: The Northwest CRP reviewed 13 radiation therapy facilities in the period February 1980 through March 1981 and 19 facilities are scheduled for review by June 30, 1981; An estimated 10 brachytherapy source stocks will by then have been reviewed. The NWCRP review list now comprises 61 machines in 49 locations. Measurements on approximately 137 breast cancer screenees (at CBCCs) will have been performed by June 30, 1981. Two BCDDPs were paid a final visit to complete scientific information, and two breast cancer screening centers under the auspices of the CBCCP were reviewed. At NCI request, the NWCRP participated in the BRH mammography phantom evaluation project, performing a standard "BCDDP" test protocol, and acquiring images of the test phantoms at four sites. The Center's staff attended the annual all-CRP intercomparisons (April 1980 and March 1981). The NWCRP participated in workshops on Quality Assurance for technologists (25 contact hours, average attendance 14, August 1980), and in a one half-day workshop on Quality Assurance in Nuclear Medicine (January 1981). The educational project - "A Short Course on Chest Radiography" has been completed; all materials (carrousel of slides and printed matter) are ready for duplication and subsequent distribution, pending final approval by the CRP task group. The course material will be shown at the spring meeting of the NW Chapter of AAPM.

Plans: The NWCRP will exhibit "Techniques and Methods of Optimizing Chest Radiography" at the 1981 AAPM meeting in Boston. Authorization will be sought to develop a series of workshops on real time, doppler, and echocardiographic diagnostic units, and on treatment planning for Hodgkin's disease. Review visits to radiotherapy institutions will continue.

Publications:

Samulski, T., Dubuque, G.L., Cacak, R.D., Courlas, G., DeWerd, L.A., Hilko, R., Humphries, L.J., Jones, D., Masterson, M.E., Miller, D.W., Stovall, M., Wochos, J.F.: Radiation Therapy Dosimetry Reviews by the Centers for Radiological Physics. Int. J. Radiation Oncology Biol. Phys. 7: 379-383, 1981.

Jones, D., Hilko, R., Schumacher, D., and Washington, J.: Variations in the Beam Characteristics of the Varian Clinac-4 (Pb). Medical Physics (in press).

Project Officer: Winfred F. Malone, Ph.D.

From 2/1/80 to 1/31/83 FY 81: 0 (Ann. \$336,394)
John R. Cameron, Ph.D., University of Wisconsin,
3321 Sterling Hall, Madison, Wisconsin 53706

Objectives: (1) to ensure uniform high quality radiological physics practices at DRCCA supported clinical facilities which use radiation for treatment or diagnosis of cancer, (2) to establish uniformity in dose specification in radiation treatments, (3) to reduce patient dose during diagnostic examinations (mammography, computerized tomography) by improving image quality, (4) to facilitate cancer control through technology transfer in the field of medical physics, (5) to serve as an educational and consultative resource in the region, (6) to provide other physics services as requested by the Project Officer, and (7) to collaborate with other CRP's and the Coordination Program.

Accomplishments: In the period February 1980 - March 1981, the Midwest CRP completed on-site mammography physics reviews at three BCDDPs prior to their being phased out, reviewed two CBCCPs, and also visited 8 mammography facilities in conjunction with a BRH-NCI/CRP study on phantoms. The MWCRP performed approximately 30 on-site physics reviews of radiotherapy facilities, 312 mammography mailed thermoluminescent dosimeter reviews, 120 radiotherapy mailed reviews using TLD and film to monitor beam output and collimation, and evaluated brachytherapy sources at approximately 20 institutions. The MWCRP participated in the annual intercomparison of its equipment with the other CRP's. The MWCRP organized three educational symposia on the topics of brachytherapy, ultrasound and use of TLD's. The MWCRP will have published an article in the scientific literature and delivered 10 presentations at scientific meetings. The Center will have prepared and distributed three MWCRP newsletters to circa 400 Midwest radiological physicists, and provided approximately 50 consultations at the request of medical physicists, radiologists, and radiologic technologists in the region.

Plans: The MWCRP will continue to review DRCCA supported clinical facilities that are presently part of the program and any that are assigned to it in the future. The MWCRP will organize and participate in appropriate educational programs for physics and radiological community. The MWCRP is planning an exhibit on x-rays and quality assurance for presentation at a meeting of the Wisconsin Medical Association. Also a TLD workshop and Ultrasound workshop are being planned for the fall of 1981.

Publications:

Cruty, M.R., Ghilardi-Netto, T.: Evaluation of the spectral response of the Wisconsin Mammographic kVp cassette. Med. Physics, 7: 151-156, 1980.

Samulski, T., Dubuque, G.L., Cacak, R.K., Courlas, G., DeWerd, L.A., Hilko, R., Humphries, L.J., Jones, D., Masterson, M.E., Miller, D.W., Stovall, M., Wochos, J.F.: Radiation Therapy Dosimetry Reviews by the Centers for Radiological Physics. Int. J. Radiation Oncology Biol. Phys. 7: 379-383, 1981.

Project Officer: Winfred F. Malone, Ph.D.

From 2/1/80 to 1/31/83 FY 81: 0 (Ann. \$379,463)
Prakash N. Shrivastava, Ph.D., Allegheny-Singer Research Corporation,
320 East North Avenue, Pittsburgh, PA 15212

Objectives: (1) to ensure uniform high quality radiological physics practices at DRCCA supported clinical facilities which use radiation for treatment or diagnosis of cancer, (2) to establish uniformity in dose specification in radiation treatments, (3) to reduce patient dose during diagnostic examinations (mammography, computerized tomography) by improving image quality, (4) to facilitate cancer control through technology transfer in the field of medical physics, (5) to serve as an educational and consultative resource in the region, (6) to provide other physics services as requested by the Project Officer, and (7) to collaborate with other CRP's and the Coordination Program.

Accomplishments: The Mideast CRP review work for February 1980 - March 1981 period includes: site review of 42 teletherapy units at 30 DRCCA network institutions, continuous monitoring of calibration constancy between reviews by 463 checks with mailed thermoluminescent dosimeters, calibration review of about 30 sealed sources used in brachytherapy, and review of physical parameters and phantom images for 9 mammography units in 7 facilities under a BRH-NCI/CRP cooperative project. The MECRP organized or participated in the following workshops: Electron Beam Dosimetry, March 22, 1980; Brachytherapy Dosimetry and Source Intercomparison, April 26, 1980; Quality Assurance in Diagnostic Radiology, December 13, 1980; and Radiation Therapy Technology, May 8-9, 1981. The center filled over 1000 requests for the proceedings of an MECRP seminar on "Known Effects of Low Level Radiation Exposure" from USA and abroad. The MECRP maintains capability to respond to DRCCA needs and undertake activities in developing uniform standards in other areas like computerized tomography, nuclear medicine and ultrasound.

Plans: Site reviews and monitoring programs are ongoing. The MECRP is planning a one to one educational effort at community mammography facilities by mail and phone. An educational TLD intercomparison of therapy unit outputs to demonstrate need for accuracy in calibration is being planned in cooperation with the Penn-Ohio Chapter of the AAPM.

Publications:

Shrivastava, P.N.: A Model to Analyze Radiographic Factors in Mammography. Medical Physics 7, No. 3: 222-225, May/June 1980.

Samulski, T., Dubuque, G.L., Cacak, R.K., Courlas, G., DeWerd, L.A., Hilko, R., Humphries, L.J., Jones, D., Masterson, M.E., Miller, D.W., Stovall, M., Wochos, J.F.: Radiation Therapy Dosimetry Reviews by the Centers for Radio-logical Physics. Int. J. Radiation Oncology Biol. Phys. 7: 379-383, 1981.

Shrivastava, P.N.: Radiation Doses in Mammography: An Energy Balance Approach. Accepted for Publication in Radiology.

Project Officer: Winfred F. Malone, Ph.D.

From 2/1/80 to 1/31/83

FY 81: 0 (Ann. \$203,905)

Robert J. Shalek, Ph.D., M.D. Anderson Hospital, Physics Department,
Houston, Texas 77030

Objectives: (1) to ensure uniform high quality radiological physics practices at DRCCA supported clinical facilities which use radiation for treatment or diagnosis of cancer, (2) to establish uniformity in dose specification in radiation treatments, (3) to reduce patient dose during diagnostic examinations (mammography, computerized tomography) by improving image quality, (4) to facilitate cancer control through technology transfer in the field of medical physics, (5) to serve as an educational and consultative resource in the region, (6) to provide other physics services as requested by the Project Officer, and (7) to collaborate with other CRP's and the Coordination Program.

Accomplishments: The activities of the Southern CRP can be divided into three areas: physics review activities, task group activities, and educational activities. The SCRCP expects to make 20 on-site review visits by September 30, 1981. Along with the on-site visits, machine output at all therapy institutions is monitored quarterly by mailed thermoluminescent dosimeters; currently, 43 machines are monitored routinely. With regard to task group activities, the SCRCP's main involvement is with the Therapy Task Group which coordinates CRP activities with respect to radiation therapy. The most significant is the annual intercomparison meeting hosted by the SCRCP. Also as part of the Therapy Task Group activities, the SCRCP maintains a data bank which is a collection of data obtained during physics reviews by all CRP's. As of February 27, 1981, the data bank included information on 572 reviews of teletherapy machines, 1513 mailed and on-site TLD teletherapy machine checks and on-site checks of 392 batches of brachytherapy sources. Pertinent data are transferred to the Radiological Physics Center and thence to appropriate trial groups. The data continually are being updated and analyzed. Educational activities have been involved mainly with brachytherapy: The SCRCP has held two brachytherapy workshops at the Southwest Chapter of the American Association of Physicist in Medicine meetings this year.

Plans: The SCRCP believes that the efforts in therapy physics are adequate. However, expansion is foreseeable in the area of physics of diagnostic radiology.

Publications:

Samulski, T., Dubuque, G.L., Cacak, R.D., Courlas, G., DeWerd, L.A., Hilko, R., Humphries, L.J., Jones, D., Masterson, M.E., Miller, D.W., Stovall, M., Wochos, J.F.: Radiation Therapy Dosimetry Reviews by the Centers for Radiological Physics. Int. J. Radiation Oncology Biol. Phys. 7: 379-383, 1981.

Project Officer: Winfred F. Malone, Ph.D.

From 2/1/80 to 1/31/83 FY 81: 0 (Ann. \$432,768)
John S. Laughlin, Ph.D., Memorial Sloan-Kettering Cancer Center,
1275 York Avenue, New York, New York 10021

Objectives: (1) to ensure uniform high quality radiological physics practices at DRCCA supported clinical facilities which use radiation for treatment or diagnosis of cancer, (2) to establish uniformity in dose specification in radiation treatments, (3) to reduce patient dose during diagnostic examinations (mammography, computerized tomography) by improving image quality, (4) to facilitate cancer control through technology transfer in the field of medical physics, (5) to serve as an educational and consultative resource in the region, (6) to provide other physics services as requested by the Project Officer, and (7) to collaborate with other CRP's and the Coordination Program.

Accomplishments: The Northeast CRP program integrates clinical review, educational activities, and applied developmental work. In radiation therapy, for the period February 1980 through March 1981, 32 reviews were made and over 200 mailed dosimetry kits were processed. Processing of dosimetry kits is expected to continue at a similar pace, while review visits will continue at a slightly increased pace through September 31, 1981. This work has assisted participating hospitals, provided data for verifying radiation dosimetry for clinical study patients and served as a basis for formal educational programs. Discrepancies found in the reviews included: five cases of 3-9 percent discrepancies in dose rate, a number of wedge factor discrepancies including one as large as 35 percent, and a 10 percent discrepancy in the activity of a group of Ra-226 brachytherapy sources. Further investigation into these brachytherapy sources showed their encapsulation to be 1mm Pt instead of 0.5mm Pt as was thought by the institution. The NECRP reports and consultations promote correction of these problems at affiliated hospitals. The NECRP serves as a educational source for the radiological community through these reports and consultations as well as through workshops. On February 27, 1981 the NECRP held a workshop on computed tomography in Philadelphia, Pennsylvania, and on April 2, 1981 a workshop on brachytherapy in New York, New York. Both these workshops were attended by approximately 100 physicists, physicians and technologists. While the NECRP responsibility for mammography review visits and mailed exposure measurements has ended due to the phasing out of the BCDDPs, work is continuing on mammography phantom development and mammography dosimetry investigations. In the fall of 1980 the NECRP made 7 mammography reviews as part of a mammography phantom evaluation project sponsored by NCI and the Bureau of Radiological Health. During the course of these visits, the NECRP found one instance of kilovoltage 15kVp higher than indicated.

Plans: The effectiveness of combined review, education, and development in high-technology areas of radiology has been demonstrated. Future plans call for a continuation of current activities with extension into other known or suspected problem areas, such as computed tomography, chest radiography and electron beam therapy.

Project Officer: Winfred F. Malone, Ph.D.

Publications:

Samulski, T., Dubuque, G.L., Cacak, R.K., Courlas, G., DeWerd, L.A., Hilko, R., Humphries, L.J., Jones, D., Masterson, M.E., Miller, D.W., Stovall, M., Wocho, J.F.: Radiation therapy dosimetry reviews by the centers for radiological physics. Int. J. Radiation Oncology Biol. Phys. 7:379-383, 1981.

Masterson, M.E., Thomason, C.L., McGary, R., Simpson, L.D., Hunt, M., Miller, D.W., Laughlin, J.S.: Dependence of the CT Number-Electron Density Relationship on Patient Size and X-Ray Beam Filtration for Fan Beam CT Scanners. In Proceeding of the Society of Photo-Optical Instrumentation Engineers Technical Conference, Vol. 273, San Francisco, March 22-24, 1981.

From 2/1/80 to 1/31/83 FY 81: 0 (Ann. \$301,774)
Mary Louise Meurk, West Coast Cancer Foundation,
50 Francisco Street, San Francisco, CA 94133

Objectives: (1) to ensure uniform high quality radiological physics practices at DRCCA supported clinical facilities which use radiation for treatment or diagnosis of cancer, (2) to establish uniformity in dose specification in radiation treatments, (3) to reduce patient dose during diagnostic examinations (mammography, computerized tomography) by improving image quality, (4) to facilitate cancer control through technology transfer in the field of medical physics, (5) to serve as an educational and consultative resource in the region, (6) to provide other physics services as requested by the Project Officer, and (7) to collaborate with other CRP's and the Coordination Program.

Accomplishments: The Western CRP has been established, staff recruited, equipment acquired and procedures developed. The major activities have been in radiation therapy site reviews. In the first year of operation (Feb. 1, 1980 to Jan. 31, 1981) 27 radiation therapy were reviewed in 19 facilities. The mailed thermoluminescent dosimetry program has been initiated to serve the 35 radiation facilities in the western region. Problems uncovered at various facilities include: a calibration error in a measuring instrument, errors in the dose rate used clinically, distance indicator and alignment problems, non-linearity of the monitoring system with dose rate, wedge factor errors, excessive radiation transmission through beam block and calibration errors in brachytherapy sources. Eight mammographic units were reviewed at 7 institutions. Among these are the 4 sites at which the joint CRP/BRH mammographic phantom study was done. The WCRP planned, arranged and hosted a 5 day CT Workshop for the six CRP's. The purpose of the workshop was to develop review methods and test a proposed phantom on 4 different CT scanners. TL dosimeters of $\text{CaSO}_4:\text{Dy}$ - teflon imbedded discs are being tested for the Chest Radiography Task Group. The WCRP has acted as a technical resource to its community by providing intercomparisons of brachytherapy source calibrations for radium, cesium and iridium. The WCRP has acted as an educational resource by providing informal lectures on radiation safety to nurses caring for brachytherapy patients.

Plans: No change in the radiation therapy activities is expected. Continued emphasis on image quality in diagnostic radiology is envisioned. A developmental project to design and test low contrast phantoms for the evaluation of CT scanners is anticipated. The preparation of audio visual materials for the training of the brachytherapy nursing staff in radiation safety will be completed.

Project Officer: Winfred F. Malone, Ph.D.

Contract 05522: Training Programs for Maxillofacial Prosthodontists and
Maxillofacial Dental Technicians

From 10/01/80 to 06/29/82 FY 81: 0 (Ann. \$203,380)

Dr. Joe B. Drane, M.D. Anderson Hospital and Tumor Institute 6723 Bertner Avenue,
Houston, Texas 77030

Objectives: Accomplishment of the major objectives of this contract is expected by the end of the contract period. These objectives include the training of graduate prosthodontists in the specialty field of maxillofacial prosthetics; the training of qualified dental laboratory technicians in the fabrication of prosthetic devices and appliances necessary in the treatment and rehabilitation of head and neck cancer patients; and the training of prosthodontists in the management of complications of the oral cavity of patients treated by radiation and/or chemotherapy. The accomplishment of those goals will increase the number of thoroughly trained, much needed, personnel in this important area of the quality management and rehabilitation of cancer patients.

Accomplishments: During the first nine months of the contract period, much of the original objectives has been accomplished. Qualified prosthodontists and qualified dental laboratory technicians were recruited for the first year of the program; the curriculum was reviewed and modified to improve the overall course content; A standardized, objective, evaluation for the training program was created. This assures uniformity for satisfactory evaluation of the trainees program: The training program has been in continuous operation since July 1, 1980 and has included for the three dental residents a nine month total of:

- Maxillofacial prostheses - 177
- Patient appointments - 1,772
- Assisted with major operations - 53
- Studied patients on hospital ward - 126
- Reviewed consultations for patients on all other services - 65

All of these clinical activities were on cancer patients.

The residents attended the following conferences:

- | | |
|-------------------------------|-----|
| - Surgical Planning | 72 |
| - Radiation Planning | 76 |
| - Dental Oncology Seminar | 84 |
| - Cleft Palate Conferences | 14 |
| - Dental Oncology Workshop | 74 |
| - Literature Review | 32 |
| - Dental Oncology Conferences | 120 |

Depending on the individual resident they have spent between 245 and 130 hours reading medical and dental literature. They have devoted between 30 and 110 hours to their research projects. The titles of their research projects are:

- The role of the dental oncologist in total treatment of the cancer patient.
- Development of radiopaque methylmethacrylate implant material.

Project Officer: Lawrence D. Burke

- The effect of autoclaving on the physical properties of Silicone.

The dental residents and the technician trainees attended and participated in a complete Maxillofacial Orientation course which involved the entire month of July. This course included lectures, slide demonstrations and laboratory periods where technique cases representing obturators, chrome castings for removable prostheses, implant prostheses, complete dentures and facial prostheses were fabricated. Following the orientation month, the technician trainees have rotated through the maxillofacial intraoral laboratory, the trauma congenital chrome laboratory and the extraoral facial laboratory, and observed and participated in the fabrication of all types of prostheses. They also continue to attend appropriate lectures and presentations on Monday and Thursday mornings.

Plans: During the last three months of this first year, the residents and technicians will continue their assigned activities and attendance at lectures and seminars. All three residents and all three technicians have accepted maxillofacial positions at other institutions to which they will report upon completion of their training. New trainees for the second year of the program have been selected and have accepted their appointments.

Contract 05523: Training Program for Maxillofacial Prosthodontists and Dental Technicians

From 10/1/80 to 6/25/82

FY 81: 0 (Ann. \$109,975)

Dr. Norman G. Schaaf, Health Research Incorporated, 666 Elm Street,
Buffalo, New York 14263

Objectives: Of this proposal are twofold (1) to provide for the training of additional prosthodontists in the use of maxillofacial prostheses for the rehabilitation of patients with cancer of the head and neck and (2) to provide for the training of additional maxillofacial dental technicians in the fabrication of prostheses and appliances necessary to the rehabilitation of patients with head and neck cancer. These objectives are a recognition of the need for more trained specialists in this sub-specialty of prosthodontics. Since this proposal simply involves the expansion of an already ongoing program, fulfillment of the objectives and implementation of the program will be completed without difficulties.

Accomplishments: A training program in maxillofacial prosthetics has been expanded to include the training of three residents and two technicians each year. Since this contract is dealing with an expansion of a pre-existing training program, the transition into increased activity was smoothly carried out. Seven specific accomplishments of the project have been achieved. They are (1) sixteen lectures and seminar have been presented in the area of maxillofacial prosthetics and related subjects (2) one hundred and forty-five teaching cases will have been completed by the residents and trainees (3) sixteen specific training, practical projects have been completed by the laboratory trainees (4) four formal, graded didactic courses will have been completed by the residents and trainees (5) six oral examinations in the mode of the American Board of Prosthodontics will have been taken by both the residents and trainees (6) weekly patient review conferences are being held for the purpose of teaching, treatment planning, case review and critique.

Plans: As the project extends into its second year of funding the plans to continue the expanded training program are being formulated. For the second year (1981-1982) a total of three maxillofacial prosthetic residents and two maxillofacial dental technicians will be trained.

Publications:

Besette, R.W., Casey, D.M., Shatkin, S.S., Schaaf, N.G.: Customized Silicone Rubber Maxillofacial Implants. Annals of Surgery, March 1981. (IN PRESS)

Besette, R.W., Cowper, T., Shatkin, S.S., Schaaf, N.G.: Histologic Evaluation of Shape and Pore Size in Silicone Implants in Rhesus Monkeys. Annals of Surgery, March 1981. (IN PRESS)

Carl, W.: Oral and Dental Care for Cancer Patients Receiving Radiation and Chemotherapy. Quintessence International, March 1981. (IN PRESS)

Project Officer: Lawrence D. Burke

Ravel, P., Schaaf, N.G.: Custom Fabricated Silicone Rubber Implants for Tissue Augmentation-A Review. Journal of Prosthetic Dentistry, No. 4, Vol 45, April 1981.

Carl, W.: Dental Management and Prosthetic Rehabilitation of Patients with Head and Neck Cancer. Head and Neck Surgery Journal, Vol. 3: 27-42, September/October 1980.

Ravel, P., Schaaf, N.G., Kielich, M.: Fabrication of Perforated Silicone Rubber Implant. Journal of Prosthetic Dentistry, Vol. 45, No. 4, April 1981.

Contract 05524: Training Program for Maxillofacial Prosthodontists and
Maxillofacial Dental Technicians

From 10/01/80 to 6/30/82 FY 81: 0 (Ann. \$105,416)

Dr. Mohamed A. Aramany, Eye and Ear Hospital of Pittsburgh, 230 Lothrop Street,
Pittsburgh, Pennsylvania 15213

Objectives: To train prosthodontists and technicians in the field of maxillofacial prosthetics with special emphasis on cancer patients. The existing residency program was expanded by one additional resident and a technician training program of a 12-month duration was reinitiated. Three technician trainees were accepted in this program for year one of the contract and an additional three technicians will be accepted for the second year of the training program.

Accomplishments: All residents and technician trainees were selected and started their program for the first year of the program 1980-1981. Their training proceeded very smoothly and will be completed by the end of June 1981.

During the first year of the contract, three technicians and one resident completed their training program. Two additional residents graduated from the three-year program.

Participation in predoctoral oncology educational program - junior dental students spend 20 clinic hours each at the Maxillofacial Center. Lectures were given to predoctoral dental students, dental hygiene and dental assistant students. Presentations have been given at the American Academy of Maxillofacial Prosthetics in San Antonio, Texas and the American College of Surgeons in Atlanta, Georgia on cancer of the head and neck as well as lectures to local groups of physicians and dentists on our oncology curriculum and training program. An upcoming presentation in September 1981 will be given to the American Prosthodontic Society in Kansas City, Missouri.

From October 1980 to date, we have treated 85 cancer patients and anticipate a total of 150 to September 1981. These are new patients that were seen at Eye and Ear Hospital only. The other facilities including Western Pennsylvania Hospital and the Veterans Hospital have seen 109 new cancer patients from October 1, 1980 to date and anticipate seeing a total of 200 patients to September 1981. Patient visits from the three facilities from October 1, 1980 to date total 3,000. The sites of cancer in the new patients treated include floor of the mouth, tonsil, maxillary sinus, nose, mandibular, neck, larynx, soft palate, ear, and tongue.

Plans: To complete the selection of the candidates for both programs. This is to be followed by repeating the educational and clinical curriculum for the new trainees. Additional publications are in preparation with active participation of the trainees. We will assist the trainees in preparing their resumes and developing a kit showing the areas of their expertise to be used in applying for jobs. This will include examples of intraoral and extraoral prostheses.

Selection of trainees is being conducted currently for the technician training program. This process will be concluded by the end of April 1981. Three technicians will be selected and will start their program on July 1, 1981. The

Project Officer: Lawrence D. Burke

resident selection for a prosthodontist is also underway. Criteria of graduate admissions of the School of Dental Medicine are followed with this process.

Publications:

Aramany, Mohamed A.: Maxillofacial Prosthodontic Rehabilitation for Head and Neck Cancer Patients. In Cancer of the Head and Neck. Churchill and Livingstone, 1981.

Deutsch, Melivn, M.D., Oral, Koray, D.M.D., M.S., Aramany, Mohamed A., M.S.: Silicone Radioactive Seeds Carrier for Nasal Neoplasm. Journal of Prosthetic Dentistry (IN PRESS)

Aramany, Mohamed A., D.M.D., M.S., Downs, Jane, D.M.D., Beery, Quinter, Ph.D., and Aslan, Yavuz, D.M.D., Prosthodontic Rehabilitation for Glossectomy Patients. Journal of Prosthetic Dentistry (IN PRESS)

Contract 05525: Community Hospital Oncology Program - Southwest Washington Hospitals

From 09/30/80 to 06/30/82 FY 81: 0 (Ann. \$82,100)
Dr. Richard Heitsch, Southwest Washington Hospital, P.O. Box 1600,
Vancouver Washington 98668

Objectives: Major objectives of the project are: (1) To develop and document medical, nursing and rehabilitation/supportive care management guidelines for each of the six major cancer sites; (2) To establish a system and procedures for identifying appropriate cancer patients for entry into the program and for ensuring their review against multidisciplinary management guidelines; (3) To develop interdisciplinary programs in cancer rehabilitation, supportive care, and terminal care; (4) To disseminate up-to-date cancer management information to community physicians, nurses and other health professionals; (5) To develop a data management and evaluation system for the review of cancer management practices and patient outcomes, as well as program accomplishments and effectiveness.

Accomplishments: Significant accomplishments or major activities to be accomplished include: (1) program administrative and organizational structure has been established, with the hospital cancer committee appointed as the policy-making board and the technical review committee. Sub-committees formed to assist the cancer committee include physician site-specific management guideline committees, a community cancer nursing committee, a community continuing care committee, and an evaluation committee; (2) physicians admitting and/or treating 75% of cancer patients in the community have been identified; site committee membership was selected from this list. Six initial cancer sites were selected on the basis of incidence, representing 58% of all new cancer patients; (3) physician, nursing, and rehabilitation/supportive-care guidelines will be developed; a system and procedures for selecting cancer patients to be entered into the program and for ensuring their review against the guidelines will be established; (4) information contacts and referral arrangements are being established with graphically appropriate cancer centers and other specialized management resources; (5) Two oncology nurse coordinators have been selected for the program and are receiving specialized oncology training. These nurse oncologists have provided patient and supportive-care services to approximately 100 patients from October 1980 through March 1981, as well as community education and information programs; (6) interdisciplinary programs and services in rehabilitation, supportive care, and terminal care are being planned; (7) a plan for the ongoing identification and dissemination of up-to-date cancer management information to physicians, nurses, and other community health professionals is being formulated; (8) a community advisory committee is being formed to assist in promoting and marketing cancer programs and services, and to assist in fund raising.

Plans: Additional plans and expected outcomes through the planning phase (through June 30, 1982) include: (1) preparation and submittal of a comprehensive implementation plan by December 30, 1981; (2) Oncology nurses to complete specialized training; (3) specialized training for other health professionals to have a significant role in programs or services to be started or completed; (4) necessary activities will be completed in preparation for the implementation of planned services and programs.

Project Officer: Donald N. Buell, M.D.

Contract 05526: Community Hospital Oncology Program - Georgia Baptist Hospital

From 09/30/80 to 03/31/82

FY 81: 0 (Ann. \$87,667)

Dr. Mario Ravry, Georgia Baptist Medical Center, 300 Boulevard, N.E.,
Atlanta, Georgia 30312

Objectives: The overall objective of this program is the improvement of the scope and quality of cancer care through a model approach to the organization, development, implementation and evaluation of community hospitals cancer care program.

The specific objectives are to develop patient management protocols (PMP), develop appropriate and complete pretreatment evaluation, develop mechanisms to assure that PMP's are available in the community and that multidisciplinary disciplines are incorporated into patient management decisions, develop oncology nursing procedures, develop a hospital/community resources program for rehabilitation and supportive care, develop a continuing care program for the terminally ill, develop a professional education program, expand the cancer data management system, develop an evaluation plan and develop a community-endorsed plan to continue the cancer care program after the federal funding ceases. Scientific evidence will be provided to show that the implementation of this program effects a change in medical practice.

Accomplishments: Each of the objectives is addressed in terms of planning and mechanisms of implementation and evaluation. Necessary administrative and professional staff have been recruited and available professional and allied health personnel needed to create and implement a multi-disciplinary clinical oncology program have been identified. Appropriate committees to direct and plan the program have been established. Protocol site committees have been formed for the development of patient management guidelines. Flow charts from the patient management protocols will be placed in every patient chart. The nursing committee has been reviewing patient care plans, medication protocols and evaluation-discharge plans. The discharge plans will be presented to the Rehabilitation Committee for their review.

Plans: A preliminary data management plan has been formulated. Planning will continue. Educational and liaison activities will be strengthened.

Project Officer: Dorothy R. Brodie, M.D.

From 09/30/80 to 6/31/82

FY 81: 0 (Ann. \$103,000)

Dr. Thomas G. Lutz, Deaconess Hospital, 600 Mary Street, Evansville, Indiana 47710

Objectives: Our major accomplishments should affect both patient and care-providers. For the patients, we anticipate improved pretreatment evaluation and more encompassing therapy on first treatment contact. Additionally, the contract will organize community resources to be more accessible for patient utilization. For care-providers, we anticipate educational benefits affecting practice habits and improving patient care. Participation on Site Committees will increase physicians' knowledge about the diagnosis, treatment, and care of patients and thus transfer to daily practice. The development of readily available guidelines will provide information when it is needed to those care-providers inexperienced in these diseases.

Accomplishments: For the period ending September 30, 1981, we anticipate a number of major accomplishments:

1. We will involve the physicians who admit more than 75% of the cancer patients to Deaconess Hospital. Thus those physicians most intimately involved in the care of cancer patients will be most directly affected by this program. Transfer of current information directly to patient care should be immediate.
2. We will develop Sites-specific guidelines in ten (10) areas: Brain, Breast, Colon/Rectal, Gynecologic, Head and Neck, Hematologic, Lung, Melanoma, Upper Gastrointestinal, and Genital Urinary. More than sixty-one (61) physicians representing at least thirty-six percent (36%) of the active hospital staff will participate on these Site Committees.
3. Site-specific nursing standards will be developed parallel to those developed by the physicians. The nursing committees formed have fifty-six (56) nurses, most of whom are directly involved in the care of cancer patients. Like the physicians, changes in care should be immediate.
4. A liaison has been formed with the following University-based referral centers surrounding Evansville: St. Louis University and Washington University in St. Louis, Missouri; the University of Louisville in Louisville, Kentucky; and Vanderbilt University in Nashville, Tennessee. This will enable more direct referral of patients and more appropriate information feedback to physicians on their patients' return.

Plans: Our planning at this time is directed toward completing tasks currently underway: Completion of physician and nursing guidelines, development and completion of a patient information booklet, as final planning for the terminal care program, and final drafting of our data management evaluation plan.

Project Officer: Donald N. Buell, M.D.

Contract 05528: Community Hospital Oncology Program - Penrose Hospital

From 09/30/80 to 06/31/82 FY 81: 0 (Ann. \$79,800)
Dr. Paul N. Anderson, Penrose Hospital, 2215 N. Cascade Avenue,
Colorado Springs, Colorado 80907

Objectives: The major objectives of the Southern Colorado Cancer Program, a consortium of four hospitals are (1) to establish and sustain a cooperative community-wide cancer program through the development of a medical and scientific program which will ensure a comprehensive multidisciplinary approach to the spectrum of cancer patient care, (2) to further develop and maintain a mechanism to ensure that cancer nursing procedures are of the highest quality through the training of oncology nurses, (3) to develop and maintain community resources that will meet the needs of cancer patients, (4) to develop ongoing educational programs to ensure medically and scientifically appropriate information is continuously available, and (5) to develop a comprehensive evaluation of the program and its impact on patient management, patient outcome, and participants.

Accomplishments: Physicians treating 75% of all cancer patients in the community were identified. Major sites to be addressed have been selected and multidisciplinary specific site committees for the development of guidelines are established. Guideline books will be made available to individual physicians and participating institutions. Two site committees have completed guidelines to date.

An assessment of attitudes, knowledge and specific nursing training needs was initiated by the nursing committee. Specific nursing standards, criteria, and educational programs for the care of cancer patients will be developed.

A Rehabilitation, Social Services and Continuing Care Committee has been established to assess the present level of community services available to cancer patients and their families. The major product of this committee will be the improvement in services for cancer patients and their families through further work with community agencies.

The Palliative and Terminal Care Committee has been established to assess the need in the community as seen by physicians, hospitals, nursing home administrators, and practicing registered nurses. The product of this committee will be the further cooperative development of the Pikes Peak Hospice to meet the identified community-wide need for palliative and terminal care.

A plan for the data management for participating institutions is being developed by the Data and Evaluation Committee to enable participants to assess the degree of participation in the community and evaluation of the Community Hospital Oncology Program (CHOP). A specific evaluation plan developed in cooperation with other CHOP programs around the nation will be developed to provide measurable products regarding process, impact, and outcomes of the CHOP programs.

Plans: Planning for the completion of various projects now underway will culminate in the development of an implementation plan by September 30, 1981. This will include the wrap up of the site specific guidelines and the distribution of those

Project Officer: Dorothy R. Brodie, M.D.

guidelines for review, the identification of educational needs for professionals and the evaluation of community resources for social services, rehabilitation, and continuing care, and a cooperative data system and evaluation plan for the national CHOP effort will have been developed.

Contract 05529: Community Hospital Oncology Program - Our Lady of Lourdes Hospital

From 09/30/80 to 06/31/82

FY 81: 0 (Ann. \$82,400)

Dr. Robert E. Enck, Our Lady of Lourdes Hospital, 169 Riverside Drive,
Binghamton, New York 13905

Objectives: The purpose of the Community Hospital Oncology Program (CHOP) is to field test a model for the development of a multi-disciplinary clinical oncology program, and to provide scientific evidence that the implementation of a CHOP model, in a community, will improve the scope and quality of care for cancer patients. The major objectives include: 1) defining criteria for cancer patient care through the development of multi-disciplinary patient management plans, 2) planning and implementing the program to encourage community cancer care practices in accordance with the criteria for care, and 3) use of a data management system to access the extent to which community cancer care practices correspond to the the developed criteria, then use this information to correct, modify and improve the program and document changes in community cancer care.

Accomplishments: As a result of activities under this contract effort, a series of site specific, multi-disciplinary patient management plans for the staging and medical management of the most frequently seen cancers have been developed. These guidelines were prepared through the work of seven site committees.

Allied health professionals serving on the Rehabilitation and Support Committee have developed site specific rehabilitation management guidelines, identified community resources available to cancer patients, and participated in the development of educational materials. Emphasis is now being placed on analyzing the utilization of services and evaluation of current rehabilitation and social service practices in the community.

A clinical nurse specialist in Oncology and an oncology nurse are working fulltime with the CHOP. The nursing committee has completed and published site specific nursing guidelines for the care of patients with cancer. In addition to being very active in educational programs, the Nursing Committee is developing a nursing audit and evaluation plan.

A computerized cancer data system has been implemented. This system which includes the tumor registry will be used to document program accomplishments and effectiveness, assess community cancer care practices and patient outcome status. Additionally, in collaboration with other CHOPs, an evaluation plan has been prepared by which the operation and impact will be assessed.

While this program is a single hospital model, it has developed a rural outreach component with seven area hospitals. Personnel from these hospitals have been active in providing support and input to the various committees, and have been involved in the CHOP's educational programs.

Plans: Activity will now focus on implementing the plan that has been developed with emphasis being placed on data collection and evaluation of the operation and impact. Committees will continue to meet and update the patient management plans, develop audit documents, and educational activities and programs.

Project Officer: Dorothy R. Brodie, M.D.

From 09/30/80 to 06/30/82

FY 81: 0 (Ann. \$78,320)

Dr. Robert H. Greenlaw, Marshfield Medical Foundation, 1000 N. Oak,
Marshfield, Wisconsin 54449

Objectives: The Marshfield Community Hospital Oncology Program will design, implement and evaluate a model for cancer control in a large, single complex of institutions having both an active in-house oncology commitment and a large, multi-specialty group with an out-patient involvement. Health care providers will collaborate to define guidelines dealing with medical care, nursing care, rehabilitation, and psychosocial adaptation which represent issues of concern in the process and outcome of care. During the current period, the planning process will be nearing completion which will involve development of implementation and evaluation plans. During a two-year implementation period, the program will assess whether or not the issues of concern as defined by providers are met, and whether or not the issues of concern have had impact on the process of care and outcome of management.

Accomplishments: Between October 1, 1980 and September 30, 1981, the Marshfield Community Hospital Oncology Program will have accomplished the following:

- a. Administrative and professional staff including a full time administrative director and full time program secretary have been recruited. The professional and allied health personnel who are needed to create and implement a multidisciplinary Community Hospital Oncology Program have been identified. This section includes the physicians responsible for the admission of 75% or more of cancer patients to the hospital and the involvement of the community nursing leaders.
- b. The major committees which are needed to direct and plan the program have been established. These committees include an Advisory, Executive, Evaluation, eight Cancer Site (representing 14 to 16 cancers), nursing, rehabilitation, and patient supportive care and terminal care.
- c. Educational and referral relationships with the clinical cancer center in Madison, Wisconsin will be established and strengthened.
- d. The existing Tumor Registry will be upgraded and a Data Management System developed to measure the change in the cancer care practices at Marshfield based on the Tumor Registry.
- e. A feasibility plan for a terminal care program will be developed.
- f. Prior to September 30, 1981, an implementation plan to field test the Community Hospital Oncology Program will be developed. The plan will include a summary of planning activities, how new cancer patients will be identified, how patients will be entered into the program, which cancer sites will be addressed by the Marshfield Community Hospital Oncology Program, how multidisciplinary management decisions will be developed, the specific cancer center relationships, the oncology nursing component, the rehabilitation and

Project Officer: Dorothy R. Brodie, M.D.

supportive care programs, the continuing care program, description of how a retrospective view of cancer patient care involving the Data Management System will be accomplished, the specific educational activities, description of a plan for continuation of the program after federal funding ceases, and a finalized evaluation plan.

Plans: The Marshfield Community Hospital Oncology Program has developed plans to: complete the formation of all related Community Hospital Oncology Program committees, develop the related medical, nursing, rehabilitation, and supportive care guidelines, develop an evaluation plan, develop an implementation plan and establish stronger educational and referral relationships with the clinical cancer center.

From 09/01/79 to 02/28/85

FY 81: \$22,576

Dr. David T. Carr, American College of Surgeons, 55 East Erie Street,
Chicago, Illinois 60611

Objectives: The objectives of the American Joint Committee on Cancer are as follows:

- 1) To develop and update staging systems for malignant diseases to aid in the selection of treatment, to assist in estimation of prognosis, to improve communications regarding patients, and to assist in comparison of groups of cases from various institutions and different periods of time;
- 2) to encourage the use of the staging systems;
- 3) to cooperate with other groups interested in classification of cancers;
- 4) to develop and encourage the use of specific site data collection forms;
- 5) to evaluate biologic markers and other characteristics important in the classification of cancer; and
- 6) to evaluate the cost-effectiveness of various tests used in staging patients before treatment and in follow-up studies after treatment.

Accomplishments: Since October 1, 1980, the American Joint Committee on Cancer has continued to distribute the Manual for Staging of Cancer as well as separate fascicles on: Reporting of Cancer Survival and End Results and Staging Systems for Cancer at Gynecologic Sites. In addition, separate fascicles on Staging Systems for Soft Tissue Sarcoma, Staging of Lung Cancer, and Staging of Head and Neck Sites and of Melanoma, have been published and are in the process of wide distribution.

At the Annual Meeting in January 1981, reports of the accomplishments of the task forces were presented and preparations for a revision of the manual were discussed. It is anticipated that the new manual will be published and distribution begun by the end of 1981. Separate fascicles on breast cancer, malignant bone tumors, staging of tumors of the central nervous system, gastrointestinal sites and urological sites will be prepared, as well as for inclusion in the Manual for Staging of Cancer 1981.

A Position Paper on Screening for and Staging of Cancer was published in the Journal CA as well as in the Bulletin of the American College of Surgeons.

Two additional task forces have been appointed for the staging of tumors of the eye and staging of tumors of the liver and biliary tract.

Plans: The American Joint Committee will continue to develop and upgrade cancer staging systems as well as disseminating the information for use by the medical profession in improved staging of cancer.

Program Director: Donald N. Buell, M.D.

Revised and updated data collection forms are being included in the new manual as well as recommendations regarding appropriate staging procedures.

Publication of the new manual is anticipated in late 1981. 25,000 copies will be printed in addition to fascicles on pediatric malignancies, breast cancer, malignant bone tumors, brain tumors, gastrointestinal sites and urologic sites.

Grant 14134: Automated Urinary Cytology for Cancer Detection

From 12/01/72 - 11/30/81

FY 81: \$141,382

Dr. M.R. Melamed, Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021

Objectives: The primary objective of this project is to develop and evaluate a flow cytometry system for detecting and characterizing carcinoma of the bladder by automated examination of exfoliated epithelial cells obtained by saline barbitage. An automated flow cytometry system provides a means for rapidly measuring multiple photometric properties of individual cells in fluid suspension as they stream through a beam of light. Under proper conditions of staining with the metachromatic fluorescent dye acridine orange, it is possible to objectively quantitate nuclear DNA and cytoplasmic RNA in each cell, and to measure nuclear (or cellular) diameter. Subsequent analysis of these data permits identification of dead or dying cells, normal bladder epithelial cells, squamous cells, granulocytes and tumor cells. The interpretation of each specimen is recorded on a computer-generated hard copy replica of the two-dimensional scattergrams, or pseudo-three-dimensional projection of the data, and used as a permanent report of that specimen.

Accomplishments: Since March 1979 over 1000 specimens from more than 400 patients have been studied. The criteria for recognizing bladder cancer depend on: (1) the presence of an aneuploid stem cell line, or, (2) the presence of a tetraploid stem cell line with greater than 15% hyperdiploid cells. A suspicious sample depends on: (1) the presence of a tetraploid stem cell line with 10% to 15% hyperdiploid cells, or (2) greater than 10% hyperdiploid cells with no aneuploid stem cell line. A negative specimen is one with less than 10% hyperdiploid cells and no aneuploid stem cell line. A summary of some of our results using these criteria are presented.

Study of normal and non-neoplastic bladder diseases.

	<u>BPH</u>	<u>NON-UROLOGIC NEOPLASMS</u>	<u>PROSTATE CARCINOMA</u>	<u>CHRONIC CYSTITIS</u>
<u>FCM RESULTS</u>				
Positive	0	0	0	2
Suspicious	0	0	9	22
Negative	22	18	17	10
Total	22	18	26	34

The false positive rate for this group of patients was 2%.

Program Director: William E. Straile, Ph.D.

Study of histologically proven cases of bladder tumor.

<u>TUMOR</u>	<u>NO.</u>	<u>FCM-POS</u> <u>NO/%</u>	<u>FCM-SUSP</u> <u>NO/%</u>	<u>FCM-NEG</u> <u>NO/%</u>	<u>ANP/%</u>	<u>TET/%</u>
Papilloma	36	11/31	12/33	13/36	6/55	5/45
Pap CIS	35	30/86	4/11	1/3	12/40	18/60
Flat CIS	71	69/97	0/0	2/3	58/84	11/16
Invasive	52	48/92	3/6	1/2	32/67	16/33

The false negative rate for this group of patients was 18%, 7% if papilloma is excluded.

Flow cytometric evaluation of saline bladder irrigation specimens is a sensitive and specific method of detecting the presence of bladder carcinoma. It is at least as sensitive as conventional urine cytology, is objective, quantitative, reproducible and requires minimal technical skill.

Plans: The last several years have seen substantial improvements in flow cytometry instrumentation, a better understanding of the useful DNA probes and much more sophisticated computer data analysis techniques. As a result, features of interest in exfoliated bladder epithelial cells now can be measured with a high degree of precision.

The presence of carcinoma is identified by the distribution of measurements of DNA in the several thousand cells per sample. Nearly 400 patients have been studied, so far. Flow cytometry was positive in 147 of 158 patients with carcinoma or carcinoma in situ, and suspicious in 7 others (2 1/2% false negative). It was positive in 1/3 and negative in 1/3; what this signifies regarding prognosis is still not known. Of 100 control patients without bladder neoplasms only 2 had positive flow cytometry - both with severe cystitis, calculi and squamous metaplasia.

The quantitative nature of flow cytometry also provides a measure of extent of disease. In sequential examinations over time it may indicate progression, or response to treatment. Flow cytometry examinations have been particularly helpful in following patients who are treated conservatively for low stage bladder tumors, or by intravesical BCG immunotherapy for carcinoma in situ.

Thus, it appears that flow cytometry now can be introduced, cautiously, into the clinical management of patients with neoplasms of the urinary bladder.

From 12/01/72 to 11/30/81

FY 81: \$191,194

Dr. W.H. Chapman, University of Washington, Seattle, Washington,

Objectives: To analyze bladder tumor cell surface antigens with serological techniques and study immunoregulatory mechanisms with an eye toward immunotherapy. To raise monoclonal antibody to several antigens of bladder carcinomas in mice, rats and humans. To characterize antigens biochemically and test antibodies for localization in growing tumors and usefulness in carrying destructive agents or modifiers of tumor activity.

To increase the efficiency of Staphylococcus aureus as an immunostimulant against growing bladder tumor, varying the route and schedule of administration. To treat bladder tumors with plasmapheresis and ex vivo immunosorption with Staph. aureus containing protein A and monitor the effect on circulating immune complexes.

Accomplishments: Problems with PPLO contamination in early 1980 forced us to reestablish a series of PPLO-free mouse bladder tumor lines and newly induced PPLO-free FANFT-induced bladder carcinoma in BALB/c mice. Two hybridomas have been made which define antigens strongly expressed in 50% of bladder carcinomas and not in other tissues. One defines a protein of 70,000 M.W. weight (not PPLO or MuLV antigens gp70) and the other defines a 250,000 dalton protein. Three other hybridomas forming antibodies binding to cultured bladder tumor cells but not to cultured sarcomas or fibroblasts are being tested for specificity in the nature of the antigen defined.

We have tested seven different cultured bladder tumor carcinomas and biopsies from similar tumors for the expression of melanoma associated antigen p97. They all were found to have expressed more p97 than a variety of normal tissues, but none of the bladder carcinomas expressed as much p97 as in two-thirds of the melanomas. The most reactive tumors were found to be present approximately 15,000 molecules of p97 per cell. We conclude that p97 might be useful as a marker of human bladder carcinoma as it is for several other tumors, but that we should attempt to obtain monoclonal antibodies to markers of higher degree of bladder specificity.

Rats injected with a transplantable bladder cell line were treated with Staph. aureus Cowan Strain (SAC). The SAC was completely effective in suppressing the growth of injected tumor cells when mixed with these, and it produced regression in 20-30% of established tumors. This effect could be titrated to very low levels (1 SAC to 100 tumor cells). Protein A alone was not effective and Staph. aureus Wood Strain (with no protein A) was as effective as SAC.

The technique allowing plasmapheresis and ex vivo immunosorption in the rat was developed. Preliminary experiments utilizing ex vivo immunosorption of plasma with Staph. aureus Cowan Strain have produced a consistent slowing of tumor growth although statistical significance has not been reached with the small number of animals so far treated.

Program Director: William E. Straile, Ph.D.

Plans: We will continue characterization of antigen from murine bladder tumors. The immune complexes removed by immunosorption therapy will be recovered and compared to the characterized antigens. An improved schedule of immunotherapy can then be recovered and compared to the characterized antigens. An improved schedule of immunotherapy can then be planned. Human bladder tumor antigens will be compared so that transfer to clinical therapy can be planned and monitored.

Publications:

Woodbury, R.G., Brown, J.P., Loop, S.M., Hellstrom, K.E., and Hellstrom, I., "Analysis of Normal and Neoplastic Human Tissues for the Tumor-Associated Protein p97". Int. J. Cancer 27:145-149. 1981.

Brown, J.P., Woodbury, R.G., Hart, C.E., Hellstrom, I., and Hellstrom, K.E., "Quantitative Analysis of Melanoma-Associated Antigen p97 in Normal and Neoplastic Tissues." Proc. Natl. Acad. Sci. 78:539-543. 1981.

Yeh, M-Y., Hellstrom, I., and Hellstrom, K.E. "Clonal Variation in Expression of a Human Melanoma Antigen Defined by a Monoclonal Antibody." J. Immunol. 126:1312-1317. 1981.

From 05/01/73 to 04/30/82

FY 81: \$87,058

Dr. J. Leighton, R. Nicosia, Medical College of Pennsylvania, Philadelphia, Pennsylvania

Objectives: To simulate in histophysiologic gradient culture some structural abnormalities that are seen regularly in tissues of clinical cancer when examined by the surgical pathologist. Among these abnormalities we plan to study:

- a. changes in stratified epithelium that appear as disorders of polarization, i.e. disruption of the orderly sequence of maturation from the basal to the free surface of the membrane;
- b. replacement of normal epithelium by carcinoma in the lateral spread of carcinoma-in-situ;
- c. tumor angiogenesis--the reciprocal stimulation of growth between vasculature and carcinoma;
- d. desmoplastic or desmolytic responses of connective tissues to carcinomas.

By simulating associations of cells seen in cancer tissue, we will be able to distinguish between aspects of structure that are regulated by the cells and those induced by components of the medium.

Accomplishments: Histophysiologic gradient culture uses a plastic apparatus that we developed in collaboration with the Costar Co. of Cambridge, Massachusetts. Tissue is attached to a thin collagen diaphragm with plasma clot and the diaphragm is arranged in the plastic capsule so that metabolic exchange takes place in only one direction, through the diaphragm. Thus we simulate the spatial relationship always found in mammals at the stromal-epithelial interface where three functions co-exist, attachment, complete nutritional exchange including oxygen, and the initiation of renewal of epithelium.

To simulate carcinoma-in-situ, where one epithelium may progressively replace another, we have put two epithelial inocula at opposite poles of the diaphragm. Each epithelium grew in its characteristic pattern. Living cultures were studied as the two epithelia met. In the combination of two cell lines, NBT II a squamous cell line, and MDCK a columnar epithelial line, there was apparent progressive replacement of the NBT II by the MDCK. Histologic sections transverse to the frontier zone showed MDCK attached to the diaphragm, separating NBT II from the diaphragm. By expressing a greater avidity for attachment to the physical-nutritional substrate, MDCK undermined and replaced the previous occupant.

We are studying capillary angiogenesis by culturing segments of rat abdominal aorta in a fibrin clot. In 7 to 10 days the explant was surrounded by a plexiform network of branching capillaries. Histologic, ultrastructural, and autoradiographic observations suggest that neovascularization in culture occurred in two main phases, an initial phase of longitudinal growth in which migration was coupled with proliferation along the main axis of the sprout, and a second stationary phase in which growth occurred in a cross sectional plane with formation of the lumen. Interaction between neoplastic cells and microvasculature was studied by inoculating 7-day-old cultures of rat aortas with the

Program Director: William E. Straile, Ph.D.

NBT cell line. Wherever contacts between the neoplastic cells and the newly formed vessels were established, a striking change in the pattern of growth of the NBT II cells was observed. Instead of growing as globular buddings, NBT II proliferated using the vascular bed as a supporting trellis, and followed the branching pattern of the capillaries. Light microscopic and preliminary ultrastructural studies suggest that NBT II in vitro is able not only to grow along vessels but also to destroy the vascular basement membrane and damage the endothelium, forming gaps through which intravasation occurs.

- Plans: a. To continue studies on the four objectives listed above, providing a view of the potential application of histophysiologic gradient culture to improving our understanding of certain structural abnormalities characteristic of cancer.
- b. To culture grade II clinical bladder cancer in our model system alone and in association with other tissues, such as normal rat urothelium, branching capillaries, and fibroblasts. These different conditions of culture will constitute a battery of tests that will provide new kinds of data which, when correlated with eventual clinical outcome, may improve the precision of pathologic evaluation for individual patients.

PUBLICATIONS:

Leighton, J., Tchao, R., Stein, R., and Abaza, N. Histophysiologic Gradient Culture of Stratified Epithelium. In Harris, C., Trump, B., and Stoner, G. (Eds.): Methods and Perspectives in Cell Biology. New York, Academic Press, 1980, Vol. 21B, pp. 287-307.

Leighton, J., Tchao, R., Johnson, W., and Abaza, N. Histokinetic Responses of Epithelial Cells in Histophysiologic Gradient Culture. In DeBrabander, M. (Ed.): Cell Movement and Neoplasia. New York, Pergamon Press, 1980, pp. 61-64.

Rabito, C. A., Tchao, R., Valentich, J., and Leighton, J. Effect of Cell-Substratum Interaction on Hemicyst Formation by MDCK Cells. IN VITRO, 16: 461-468, 1980.

Tchao, R. and Leighton, J. Stimulation of Cyst Formation by Dibutyryl Cyclic AMP in Human Urinary Bladder Tumors Cultured In Vitro. Cancer Research, 41: 635-639, 1981.

From 06/01/73 to 05/31/82

FY 81: est. \$36,777

Dr. A.M. Pamukcu, Department of Human Oncology, University of Wisconsin
Center for Health Sciences, Madison, Wisconsin

Objectives: The objectives of this project are to isolate, characterize and demonstrate the bladder carcinogenicity of biologically active chemicals present in bracken fern (BF), in milk of cows fed BF, and in urine of cows and rats fed BF.

Accomplishments: In an effort to characterize the BF carcinogen, we have isolated many chemicals such as isoquercitrin, rutin, astragalín, tiliroside, tannin and organic acids.

To test the carcinogenicity of BF tannin, chloroform fraction, and tannin-free aqueous fraction of BF, we administered each fraction orally to rats for 18 months. Tannin (cumulative total dose 22.5 g/rat) failed to induce either bladder or intestinal tumors in rats. Conversely, the chloroform fraction and tannin-free fraction induced intestinal tumors in 7 to 15 rats. However, repeated sc injections of tannin produced histiocytomas at the injection sites without distant metastasis. Urine of rats fed BF, the chloroform fraction, or the tannin-free fraction of BF showed mutagenic activity in S. typhimurium TA100. The carcinogenicity of BF was attributed to a chemically unknown compound rather than tannin.

To test the carcinogenicity of biologically active flavonoid compounds such as rutin and isoquercitrin in BF, flavonoid glycosides were extracted by hot methanol and purified by polyamide column chromatography following quantitative acid hydrolysis and preparative thin-layer chromatography. No free quercetin or kaempferol were present in BF. Dried BF contained (g/kg): quercetin 0.86, and kaempferol 2.55 as liberated aglycones. In view of the mutagenic activity of quercetin, we demonstrated the carcinogenicity of quercetin by administering it orally to albino rats in a grain diet at a dose of 1000 ppm for 14 months. Quercetin-fed rats developed intestinal (75%) and bladder (20%) tumors. The neoplasms produced in quercetin-fed rats were grossly and histologically identical to those produced in BF fed rats. These findings indicate that quercetin was carcinogenic for the intestinal and bladder epithelium of rats. Kaempferol obtained with the above procedure has mutagenic activity in S. typhimurium TA 98 and TA100. It is possible kaempferol in BF may have additional carcinogenic activities. Lack of availability in quantities sufficient for in vivo carcinogenesis assays has prevented this study. However we developed a new method to synthesize kaempferol with high yield and purity. Quercetin is not the only mutagen and carcinogen present in BF. There is another mutagenically-active compound (not quercetin or kaempferol). Recently, we have developed extraction and chromatographic methods to isolate this biologically-active chemical which is not related to flavonol compounds in physical and chemical properties. Its isolation is in progress.

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We found that rats fed BF excrete two different biologically active compounds in their urine. One similar compound was present in urine of rats fed quercetin or rutin. This compound was mutagenic to S. typhimurium TA98 and weakly to TA100. It had the same fluorescence and RF values (0.30, cellulose, CHCl₃-HCOOH-H₂O 50:45:5, v:v:v; 0.47, cellulose, phenol-water, 100:39, wt:wt; 0.47, polyamide, 100% methanol) on thin-layer chromatograms as an authentic sample of quercetin, and the mutagenic activity is believed to be due to excretion of unchanged quercetin. The second compound was not present in urine of rats fed quercetin or rutin. It was only mutagenic to TA100, not to TA98. This mutagen is not related to quercetin content of BF. Work is in progress to isolate and identify the unknown mutagen present in urine of rats fed BF.

We demonstrated earlier that the carcinogenicity of BF could be inhibited by various chemicals. Recently we studied the inhibitory effect of similar chemicals on the mutagenic activity of quercetin in S. typhimurium systems. Of the chemicals tested, disulfiram and polyvinyl pyrrolidone (PVP) (avg. m. wt. 10,000) gave substantial inhibition of quercetin mutagenic activity, the other chemicals such as butylated hydroxyanisole, phenothiazine, nicotinamide and calcium chloride did not appreciably inhibit mutagenicity. Disulfiram at 0.133, 0.399 and 0.665 μ mol/plate inhibited mutagenicity of quercetin, respectively by 35%, 67%, and 81% without activation, and 28%, 38%, and 53% with "S-9" activation. PVP at 200 μ g, 600 μ g, and 1000 μ g per plate gave, respectively, 50%, 66%, and 76% inhibition without activation; and 58%, 72%, 75% inhibition with "S-9" activation.

Plans: Emphasis of our studies will be centered on the identification of biologically active compounds in BF, in urine of rats fed BF, and testing them in rats for carcinogenicity.

Publications:

Pamukcu, A.M., Wang, C.Y., Hatcher, J., and Bryan, G.T. Carcinogenicity of Tannin and Tannin-Free Extracts of Bracken Fern (Pteridium Aquilinum) in Rats. J. Natl. Cancer Inst. 65: 131-136, 1980

Pamukcu, A.M., Yalciner, S., Hatcher, J.F., and Bryan, G.T. Quercetin, a Rat Intestinal and Bladder Carcinogen Present in Bracken Fern (Pteridium Aquilinum). Cancer Res. 40: 3468-3472, 1980

Article in Book:

Pamukcu, A.M. Tumors of the Urinary Bladder in Domesticated Animals. In: G.T. Bryan and S.M. Cohen (eds.), Pathology of Bladder Cancer, Boca Raton, FL, CRC Press, Inc., (In Press), 1981.

Grant 14524: Metabolic Factors Involved in Bladder Carcinogenesis

From 12/01/72 to 11/30/83

FY 81: est. \$28,925

Dr. G.T. Bryan, Department of Human Oncology, University of Wisconsin, Madison, Wisconsin

Objectives: The main objectives of these studies are to analyze the temporal molecular mechanisms by which demonstrated bladder carcinogens initiate or promote urinary bladder cancer in rats or mice. The model system utilized to investigate initiation is the 5-nitrofurylthiazole derivative N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT) and its close structural analogs. The model system used to study promotion is FANFT followed by L-tryptophan or other urotrophic substances. The hypotheses that early metabolic perturbations generated in bladder epithelium as manifested by alterations in polyamine anabolic, i.e. ornithine decarboxylase (ODC) and S-adenosyl-L-Methionine decarboxylase (SAM), or catabolic, i.e. diamine oxidase, enzymes as related to promotion stimuli is under test.

Accomplishments: To delineate the relative importance of the 5-nitrofuryl and the formylaminothiazolyl portions of the bladder carcinogen FANFT in its metabolic activation process that leads to the formation of its carcinogenic intermediate(s), three new analogs were synthesized and tested in rats. 2,2'-Amino-4,4'-bis-thiazole (ABT), 2,2'-formylamino-4,4'-bis-thiazole (FABT), and 2,2'-acetylamino-4,4'-bis-thiazole (AABT) containing the thiazole portion of carcinogens 2-amino-4-(5-nitro-2-furyl)thiazole (ANFT), FANFT, and N-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide (NFTA), respectively, were fed to weanling Sprague-Dawley female rats for 46 weeks at equimolar doses and all survivors were killed by 66 weeks for a complete necropsy and histologic evaluation. Our previous studies showed that the nonnitro analogs of FANFT, ANFT, and NFTA were devoid of carcinogenicity and the antibacterial activity furnished by the nitro group. This study resulted in the production of 1 fibroadenoma in 29 controls while ABT induced multiple tumors in 14 of 28 rats ($p < 0.001$) of which 6 were mammary adenocarcinomas, 8 fibroadenomas, 2 perianal and 1 salivary gland tumors in addition of 2 cases of severe transitional cell hyperplasia of the bladder; while AABT (4/29) and FABT (1/29) did not induce statistically significant tumor incidences. These results indicate that the aminothiazole portion in the free amine form may have some limited carcinogenic activity, and may have a possible role in the organotropic carcinogenicity of the FANFT molecule towards the urothelium. However, the molecular carcinogenic basis still resides with the 5-nitrofurans.

To study the mechanism of carcinogenic action, a simple analog of FANFT, 4-(5-nitro-2-furyl)thiazole (NFT) that is devoid of the formylamino moiety, was selected and tested in rats as described above. After histologic evaluation, 46 neoplasms (24 multiple mammary fibroadenomas, 19 forestomach squamous cell carcinomas, and 3 other malignancies) in 31 of 35 surviving rats were detected. 14 C-Labeled NFT was synthesized and intragastrically injected into rats. After 48 hr. 32% of radioactivity was recovered in urine, 57% in the gastrointestinal contents and feces, and 5.5% in the expired CO_2 . Collected urine, extracted with chloroform:diethyl ether and analyzed by gas chromatography (GC), provided a major peak with a retention time of about 4 min. Catalytic hydrogenation of NFT with palladium on activated charcoal

Program Director: William E. Straile, Ph.D.

afforded a product with an equal retention time. The isolated urinary metabolite of NFT exhibited similar mass spectral fragmentation patterns, in addition to the GC and high pressure liquid chromatographic retention times, as that of the chemical reduction product. These results indicate the identical chemical character of the in vivo NFT metabolite and reduction product which was spectroscopically identified as 1-(4-thiazolyl)-3-cyano-1-propanone (TCP). This was much less mutagenic for Salmonella typhimurium TA 100 than was NFT.

In addition, the induction of mouse urinary bladder ODC activity by tryptophan (TRP) metabolites (nicotinic acid, picolinic acid, quinaldic acid (QA), quinolinic acid, anthranilic acid (AA), 3-hydroxy-L-kynurenine (KYN), and xanthurenic acid (XA)), or oral L-TRP was studied. Significant differences between the mouse bladder carcinogens QA, AA, KYN, and XA induction of ODC were observed. Mouse bladder exhibited a promoting activity after oral DL- or L-TRP administration, similar to that seen in rats and dogs. These results suggest that induced bladder ODC activity may be related with the production of bladder tumors with a similar mechanism as that occurring in the skin tumor systems.

Plans: We plan to continue studying biochemical mechanisms of tissue interactions of carcinogenic 5-nitrofurans; the generation of diazonium ions in the presence of nitrite and certain endogenous primary amines; the interactions of diazonium ions with macromolecules; and the enzymatic biochemical alterations occurring after application of bladder initiating or promoting agents.

Publications:

Matsushima, M., and Bryan, G.T.: Early Induction of Mouse Urinary Bladder Ornithine Decarboxylase Activity by Rodent Vesical Carcinogens. Cancer Res. 40: 1897-1901. 1980

Takano, S., Matsushima, M., Erturk, E., and Bryan, G.R.: Early Induction of Rat Colonic Epithelial Ornithine and S-Adenosyl-L-Methionine Decarboxylase Activities by N-Methyl-N'-Nitro-N-Nitrosoguanidine or bile salts. Cancer Res. 41: 624-628, 1981.

Swaminathan, S., Erturk, E., and Bryan, G.T.: Mutagenicity and Carcinogenicity, Distribution and Nitroreduction of 4-(5-Nitro-2-Furyl)Thiazole in the Rat. Cancer Res. 41. 1981 (In Press).

From 05/01/73 to 03/31/82

FY 81: \$87,465

Dr. A.A. Sandberg Roswell Park Memorial Institute, Buffalo, New York

Objectives: The objectives of this project have been directed at establishing the chromosome constitution in bladder tumors and correlating the karyotypic findings with various clinical parameters (diagnosis, prognosis, recurrence, response to therapy), with major emphasis being placed on establishing cytogenetic parameters in those lesions (e.g., noninvasive or only submucosally invasive tumors) for which criteria of recurrence have not been well defined. In addition, studies (with a new technique) of chromosomes in transitional cell carcinoma of the bladder will hopefully reveal specific karyotypic changes, akin to those recently described in ovarian and breast cancer, thus affording an opportunity to possibly classify bladder cancers according to their cytogenetic picture.

Accomplishments: Examination of chromosomes in solid tumors has lagged behind that in leukemia and lymphoma because of the difficulty of obtaining a suitable number of metaphases for analysis. Thus, compared to the high success rate (more than 70%) in leukemia and lymphoma, chromosome data could only be obtained in less than 30% of "solid" tumors. Because of these limitations our effort during the last few years has been directed towards developing and establishing a method which would lead to much higher yields of metaphase and, hence a higher success rate in the cytogenetic analysis of bladder tumors, than has been previously available. The method we finally adopted not only yields a high success rate (around 80%), but also leads to more optimal banding of the chromosomes than afforded by previous methods. The method relies primarily on the use of collagenase II and DNase I as enzymatic approaches and yields many more metaphases (almost 10-fold) than that afforded by direct methods.

The crucial steps in the new method involve slicing of tissue with a Stradie-Riggs microtome, followed by incubation of the tissue for 2 hours with collagenase II and DNase I, repeated washings of the tissue in a petri dish, followed by pouring through a 100 mesh screen, which completes the disaggregation procedure. Cell suspensions are made from the disaggregated material and incubated for 2-5 days, with colcemid being present during the last 12 hrs. Chromosome slides are then prepared by established methodologies.

Plans: With the above method we plan to examine a large number of bladder tumors in order to (1) establish any specific karyotypic changes which may have escaped detection in the past and (2) correlate the cytogenetic findings with various clinical and therapeutic parameters of bladder cancer.

Publications:

Wake, N., Slocum, H.K., Rustum, Y.M., Matsui, S.I., and Sandberg, A.A.: Chromosomes and Causation of Human Cancer and Leukemia. XLIV. A Method for Chromosome Analysis of Solid Tumors. Cancer Genet. Cytogenet. 3: 1-10. 1981.

Program Director: William E. Straile, Ph.D.

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Sandberg, A.A.: Chromosomes as Markers in Human Cancer. In: International Advances in Surgical Oncology . Vol. 4, pp. 311-336. Ed. Murphy G.P., Alan R. Liss, Inc., New York, 1980.

Sandberg, A.A., and Wake, N.: Chromosomal Changes in Primary and Metastatic Tumors and in Lymphoma: Their Nonrandomness and Significance. In: Genes, Chromosomes, and Neoplasia, Eds. (Arrighi , F.E., Rao, P.N., and Stubblefield, E. Raven Press, New York, pp. 297-333 . 1981.

From 05/01/74 to 03/31/82

FY 81: \$132.259

Dr. R. Oyasu, Northwestern University Medical School, Chicago, Illinois

Objectives: The immediate objective of the proposed investigation is to ascertain whether urine contains a factor(s) which serves as a promoting agent(s) in urinary bladder neoplasia. Our studies are based on the hypothesis that urine may contain minute amounts of carcinogen(s) derived from either exogenous or endogenous sources and that these carcinogens induce development of cancer only when they are present in sufficiently high concentration or act in concert with a second substance(s) in urine which may serve as a cocarcinogen or a promoter. To study the role of urine in bladder carcinogenesis, a heterotopically transplanted rat urinary bladder (HTB) separated from the ureters was created in a syngeneic rat as our working model.

Accomplishments:

1. Enhancement by urine of urinary bladder carcinogenesis. The role of urine as a tumor-enhancing agent in bladder carcinogenesis was investigated by using the HTB. Bladders removed from rats initiated with the carcinogen N-butyl-N-(4-hydroxybutyl) nitrosamine (OH-BBN) in drinking water for 4 or 10 weeks were heterotransplanted to syngeneic rats. Those HTB's receiving repeated instillations of normal rat urine subsequent to transplantation had a higher tumor incidence of carcinoma (8 of 9 HTB's after four weeks of OH-BBN, and 14 to 15 HTB's after 10 weeks of OH-BBN pretreatment) than did those receiving 0.9 percent NaCl solution (0 of 9 and 6 of 13 HTB's after 4 and 10 weeks of OH-BBN pretreatment, respectively).

In a subsequent series of experiments, the above described tumor-enhancing effect of urine in the carcinogenesis of HTB was confirmed; this time N-methyl-N-nitrosourea (MNU) (0.25 mg in 0.5 ml NaCl) was instilled directly into the HTB once or three times at a weekly interval. One week after the last dose, normal rat urine or 0.9 percent NaCl was instilled into HTB weekly until the experiments were terminated at 30 weeks. The incidences of tumors in the HTB treated with urine were significantly higher than those in the HTB treated with 0.9 percent NaCl. The results indicate that urine plays a tumor-enhancing role in urinary bladder carcinogenesis and suggest that normal urine may contain tumor promoter(s).

2. In vitro induction of ornithine decarboxylase (ODC) by normal rat urine in bladder carcinoma cells (804G). The objective of this study is to determine the potential of ODC response in rat urinary bladder carcinoma cells (804G) in culture as a screening for promoters of bladder carcinogenesis. Of the various agents tested, 12-O tetradecanoyl-phorbol-13-acetate and normal rat urine induced the largest ODC response. Addition of the urine at a final concentration of 10 percent, raised the ODC activity 10 times the original level. ODC inducibility did not change when the urine was boiled for 40 minutes. The urinary components were fractionated by a Bio-Gel P-100 gel filtration column. Two peaks with high ODC inducibility were demonstrated and their approximate molecular weight is 4,300 and 37,000.

Program Director: William E. Straile, Ph.D.

Plans: Our plan for the completion of the project is to isolate the substances showing high ODC inducibility by chromatography and test them for tumor enhancing role using the HTB system.

Publications:

Hirao, Y., Izumi, K. and Oyasu, R.: The effect of normal rat urine on mucosal regeneration in heterotopic urinary bladder. Lab. Invest. 42:76-84, 1980.

Rowland, R.G. and Oyasu, R.: Permeability of heterotopic and homotopic rat urinary bladders to water, sodium and a carcinogenic aromatic amine. Urol. Res. 8:101-106, 1980.

Rowland, R.G., Henneberry, M., Oyasu, R. and Grayhack, J.T.: Effects of urine and continued exposure to carcinogen on progression of early neoplastic urinary bladder lesions. Cancer Res. 40:4524-4527, 1980.

Hirao, Y., Miyata, Y., Hearn, W.L., Radomski, J.L., and Oyasu, R.: Development of sarcomas in heterotopically transplanted rat urinary bladder unit exposed to glucuronic acid conjugate of N-hydroxy-4-aminobiphenyl. Cancer Letters 11:309-313, 1981.

Izumi, K., Hirao, Y., Hopp, L. and Oyasu, R.: In vitro induction of ornithine decarboxylase in urinary bladder carcinoma cells. Cancer Res. 41:405-409, 1981.

Oyasu, R., Hirao, Y. and Izumi, K.: Enhancement by urine of urinary bladder carcinogenesis. Cancer Res. 41:478-481, 1981.

Grant CA 14905: Study of Glycoconjugates in Colonic Neoplasia

From: 06/01/73 to 05/31/82

FY 81: \$159,086 (est.)

Dr. Young S. Kim, University of California Service, V.A. Hospital, 4150 Clement Street, San Francisco, CA 94121

Objectives: The general goal of our research program is to delineate tumor-associated changes in colonic mucosal cells and tissues with specific emphasis on alterations in structure, antigenicity, metabolism of cell surface membrane, and intracellular, and secreted glycoconjugates. The molecular basis for alterations in glycoprotein and glycolipid constituents of fetal, normal, premalignant, and malignant cells and tissues will also be clarified.

Accomplishments: Fluorescein-labeled (FITC) lectin patterns were studied in normal and cancerous colonic mucosa and in the transitional mucosa. Two of the eight lectins showed distinct differences in labeling between normal tissue and cancer. (FITC)-Dolichos biflorus agglutinin (DBA) preferentially labeled mucin of mature goblet cells of the upper crypt of normal colon, but did not label the mucin secreted by many of the colon cancers. FITC-peanut agglutinin (PNA), which failed to label the goblet cell mucin of normal colonic mucosa, showed intense labeling of the mucin of all 21 of the tumors. The goblet cell mucin of transitional mucosa and polyps showed a loss of DBA label and the appearance of PNA label, thus resembling the labeling pattern of cancerous mucins. These studies indicate that a significant alteration in the structure of mucinous glycoproteins occurs in colon cancer, and to a lesser extent in transitional mucosa and colonic polyps. The effects of sodium butyrate, dimethylsulfoxide (DMSO) and retinoic acid on the growth, morphology, cell surface membrane-associated enzyme activities and glycoprotein profiles of a human rectal adenocarcinoma cell line (HRT-18) in culture were compared. All three agents reversibly caused a marked increase in doubling times, a decrease in saturation densities and a markedly reduced colony forming efficiency in soft agar; these growth properties resemble those seen in non-cancerous cells. Only butyrate caused increased membranous process formation. These data indicate that the use of these agents may provide useful information concerning the identification of differentiation associated markers of human rectal cancer cells. Furthermore, these agents, although having similar effects on the growth properties, have different effects on the morphology and biochemical properties of human rectal cancer cells.

Plans: We plan to isolate, characterize, and develop methods to quantify the mucins and the membrane glycoconjugates that appear or disappear in colon cancer tissues. The usefulness of these methods as diagnostic or prognostic potential differentiating agents on restoring the normal growth and biochemical properties in colon cancer cells will continue to be explored for possible use as therapeutic agents.

Publications:

Kim, Y.S., Tsao, D., Siddiqui, B., Whitehead, J.S., Arnstein, P., Bennett, J., and Hicks, J.: Effects of Sodium Butyrate and Dimethylsulfoxide on Biochemical Properties of Human Colon Cancer Cells. *Cancer*, 45:1185-1192, 1980.

Siddiqui, B., and Kim, Y.S.: Fucolipids and Gangliosides of Human Colonic Cell Lines in Biochemistry of Cell Surface Glycolipids, Charles C. Sweeley, Ed. American Chemical Society Symposium Series, Vol. 128, 1980; pp. 177-186.

Program Director: Vincent J. Cairolì, Ph.D.

From: 06/01/73 to 05/31/82

FY 81: \$199,348 (est.)

Dr. M. Earl Balis, Ph.D., Memorial Sloan-Kettering Cancer Center, 1275 York Avenue,
New York, NY 10021

Objectives: Several qualitative changes occur with development of colon carcinoma. We have evaluated the qualitative and quantitative changes and have adduced evidence of their roles in the metabolism of the cancer cells. These facts may permit the design of new tests for the presence of carcinoma of the colon and for prognosis of the course of the disease. We have studied the effects of combinations of inhibitors of enzymes that are low in the tumors and have shown synergistic interactions with increased antitumor efficacy. These enzyme specificities may permit the design of combination chemotherapy that will be useful clinically.

Accomplishments: We have defined three qualitatively different enzymes in large bowel cancer. One of these, a low molecular weight form of adenosine deaminase, has been isolated and partially purified from normal colon mucosa and carcinoma. A second, thymidine kinase, has been purified. A third, phosphoribosyl pyrophosphate (PRPP) synthetase, has been identified by its membrane-bound nature. We hope to answer the question of whether or not the tumor forms are post synthetic modifications of their normal colon counterparts. Peculiarities could permit the development of new and useful markers of large bowel cancer that may be of diagnostic or prognostic value.

We have also noticed several quantitative changes in enzymes of colon tumors in mice. We are designing chemotherapeutic regimens based on these specific enzyme levels. A program has been started with the Colorectal and Chemotherapy Services of Memorial Hospital to evaluate these same enzymes in patients with large bowel cancer. In order to do this, we have had to design new assay procedures that can evaluate enzyme levels on the small amounts of tissue that can be obtained from metastatic lesions, since destruction of these is our goal.

Plans: Future research will be directed at purifying to homogeneity tumor and normal forms of thymidine kinase, adenosine deaminase, and PRPP synthetase, preparing peptide maps, seeing whether there are post synthetic modifications, and if there are any common denominators in the changes in the three enzymes. We will improve dose levels and schedules of the combinations of the drugs already tested and adapt these regimens to the clinic.

Publications:

Yip, L.C. and Balis, M.E.: Polyamine-Polyphosphate Complexes as Enzyme Inhibitors. Biochem., 19:1849, 1980.

Yip, L.C., Tedde, A., and Balis, M.E.: Effects of 2'Deoxycoformycin Infusion on Mouse Phosphoribosyl Pyrophosphate Synthetase. Biochem Pharmacol., 29:2888, 1980.

Yip, L.C., Yeh, A.K., and Balis, M.E.: Subcellular Distribution of PRPP Synthetase Activity of Rat Intestinal Mucosa. Am. J. Physiol., 239:266, 1980.

Program Director: Vincent J. Cairoli, Ph.D.

From: 06/01/73 to 05/31/82

FY 81: \$88,525

Dr. Renato Baserga, Temple University School of Medicine, 3400 N. Broad Street, Philadelphia, PA 19140

Objectives: The major objective of our project is a more precise understanding of the basic biology of the colon cells, and of the colonic carcinoma cell. More specifically, the goal of our investigations is to understand the mechanisms that regulate cell proliferation in both normal and abnormal conditions. Our interest deals with the response of the genome to the environmental factors that control cell proliferation.

Accomplishments: One of the major accomplishments in the past year has been a better understanding of the mechanisms that control the growth of cells. Specifically, we have been able to demonstrate that the growth of cells in size and cell DNA replication, two fundamental characteristics of cell proliferation, can be separated and are distinct. Growth in size of cells is independent of unique copy gene transcription, whereas the entry of cells into the DNA synthesis phase is specifically controlled by products of RNA polymerase II. The separation of growth in size and cell DNA replication is a fundamental advance in our understanding of the basic mechanisms of cell proliferation.

Plans: The planning at this point is to develop a cell line of normal colonic mucosal cells so that a rational comparison in vitro can be carried out with colonic carcinoma cells. The use of recombinant DNA and of manual microinjection should allow us to obtain colonic cell lines that can be made normal under certain precise culture conditions.

Publications:

Baserga, R.: The Cell Cycle. New England Journal of Medicine, 304:453-459, 1981.

Baserga, R.: Genes Controlling Proliferation of Mammalian Cells. Raven Press, in press, 1981.

Program Director: Vincent J. Cairolì, Ph.D.

Grant CA 14908: Nuclear Proteins in Carcinogenesis of the Colon

From: 06/01/73 to 02/28/82

FY 81: \$171,486

Dr. Vincent Allfrey, Rockefeller University, 1230 York Avenue, New York, NY 10021

Objectives: To investigate the molecular mechanisms involved in carcinogen-induced changes in chromosomal components at early stages of colonic tumor induction by 1, 2-dimethylhydrazine (DMH) including: 1) analysis of carcinogen damage to DNA and DNA-binding proteins and its dependence on chromatin structure; 2) detection of premalignant changes in nuclear protein complement and their potential as early diagnostic "markers"; 3) investigation of the reversible tumor-suppressive effects of butyrate; and, 4) development of chemotherapeutic agents which selectively inhibit tumor protein synthesis.

Accomplishments: We have observed that carcinogen damage to colonic chromosomal proteins is not random, but preferentially involves proteins in the accessible transcribing or replicating regions, such as proteins of the high-mobility group (HMG's) which are abnormally methylated (on lysine and arginine residues) following treatment with DMH. We have developed and applied high-resolution, computer-assisted 2-dimensional gel-scanning procedures for the analysis of colonic nuclear proteins at successive stages in carcinogenesis, and detected characteristic proteins which are selectively synthesized and accumulate in the colonic nuclei of DMH-sensitive mice. These proteins are not observed in DMH-resistant mouse strains. An analysis of nuclear protein phosphorylation at early stages in carcinogenesis, using these new techniques, shows that a particular nuclear protein (P55/615) is selectively hyperphosphorylated long before any morphological indications of malignancy appear. Monoclonal antibodies are being prepared against a 44 kilodalton DNA-binding protein in human colonic tumor nuclei. The mechanisms of suppression of the malignant phenotype by sodium butyrate was investigated. Butyrate inhibits the deacetylation of all nucleosomal 'core' histones and HMG proteins, and it selectively inhibits the phosphorylation of histones H1 and H2A. The phosphorylation of histones is essential for cell cycle progression; exposure to butyrate arrests cells in G₁ and prevents duplication. We have continued studies of the selective inhibition of tumor protein synthesis by sodium cyanate. It was found that cyanate "activation" by cytochrome P-450 generates a tumor-inhibitory factor. Normal cells are not sensitive to the cyanate metabolite, but all tumors so far examined, including colonic tumors of mice and men, are cyanate-sensitive. They lose that sensitivity after culture in butyrate.

Plans: We will continue the preparation of monoclonal antibodies directed against colonic tumor nuclear proteins, and test their application as "markers" of malignant transformation. The aberrant protein phosphorylations in the pre-malignant stages will be characterized further, with emphasis on whether tyrosine phosphorylation is enhanced. The reversibility of the butyrate effect will be exploited to examine which changes in nuclear protein complement correlate with the loss and restoration of the malignant phenotype. The mechanism of inhibition of tumor growth by cyanate and L-tosylamido-2-phenylethyl chloromethyl ketone (TPCK) will be investigated.

Publications: Allfrey, V.G., Boffa, L.C., and Gruss, R.: Aberrant Phosphorylation of Nuclear Proteins at Early Stages of Colon Carcinogenesis Induced by 1,2-dimethylhydrazine. J. Supramol. Struct. Cell Biochem., Suppl. 5:180, 1981.

Program Director: Vincent J. Cairoli, Ph.D.

From: 06/01/73 to 05/31/84 FY 81: \$129,351
Dr. Hans O. Sjogren, University of Lund, Fack, Lund, Sweden

Objectives: 1) To establish techniques to identify and separate monocytes and various lymphocyte subpopulations enabling analysis of selective antitumor immunity cell subpopulations and functions; 2) to characterize tumor-associated antigens including tissue-specific embryonic antigens by use of monoclonal antibodies; 3) to characterize the immunoglobulin (Ig) classes and subclasses of antitumor antibodies appearing in the course of development of dimethylhydrazine (DMH)-induced bowel carcinoma; and 4) to establish methods to induce strong tumor rejection responses with proven efficiency in prophylactic and therapeutic systems.

Accomplishments: An efficient technique to separate monocytes from lymphocytes has been developed based on differential adherence to gelatin beads in the presence of heparinized plasma. By a combination of this technique, lxx sedimentation and counter current distribution (CCD) in dextran-polyethylene glycol two phase systems, a procedure has been developed that allows the recovery of most lymphocytes in fractions depleted of monocytes and NK cells. Selective antitumor cytotoxicity has been demonstrated in such lymphocyte fractions.

The effects of histamine, a H-2 antagonist (Cimetidine) and a H-2 agonist (Dima-prit) on NK and K lymphocyte activities have been analyzed in vitro. Low nontoxic concentrations of these drugs added to target cells do not affect spontaneous ⁵¹CR-release, but do alter both NK and K cell functions. The ongoing analysis indicates that various lymphocyte subpopulations respond differently to the drugs and that augmented lymphocyte effects may be obtained.

The binding assays for antitumor antibodies of various Ig classes and IgG subclasses have been established for the rat colon carcinoma system. Confluent monolayers of viable carcinoma cells in 96-2311 plastic plates are used as targets and rabbit antisera to the various rat Ig classes and subclasses are used to detect binding of rat antibodies. This allows convenient quantitation by ¹²⁵I-labelled protein A which binds efficiently to the rabbit Ig. Anti IgA, IgG and IgM antisera and IgG subclass-specific antisera have been developed and anti IgE obtained. Sequential sera of a number of DMH-treated rats developing primary colon carcinoma have been analyzed and the same sera are now to be assayed for complement dependent cytotoxicity and antibody dependent cell-mediated cytotoxicity.

Plans: We plan to develop procedures to separate suppressor T-cells from killer T-cells; to develop adequate binding assays for H-1 and H-2 receptor bearing cells; to evaluate H-receptor agonists and antagonists as immune manipulators in concert with non-specific and specific immune stimulation; and to assess immunodiagnostic potential of assays of humoral antitumor antibodies and characterization of tumor-associated glycolipid and glycoprotein antigens by monoclonal antibodies.

Publication:

Sjogren, H.O.: Immunoprevention. In Inhibition of Tumor Induction and Development, M. Zedeck and M. Lipkin, Eds. New York, Plenum, 1981:00. 203-217.

Program Director: Vincent J. Cairoli, Ph.D.

From 04/01/74 to 03/31/82

FY 81: \$139,648

Dr. J.L. Radomski, University of Miami School of Medicine, Miami, Florida

Objectives: Only a fraction of the causative chemicals involved in the induction of bladder cancer are known. Our objective has been to search for those substances present in drugs, food additives, and the general and occupational environment so that they may be eliminated. A vital part of this search is the identification of the biochemical mechanism and structure-activity relationships of these causative chemicals.

Accomplishments: Following our previous discovery of the presence of cytochrome P-450 in bladder mucosa, we initiated a study of the ability of bladder microsomes to metabolize aromatic amines. Bovine bladder microsomes mediated NADPH-dependent N-hydroxylation of 4-biphenylamine (4-BA) at a rate of 270 nmoles N-OH-4-BA produced/nmole cytochrome P-450/min incubation, as determined by reverse phase HPLC. 2-Naphthylamine (2-NA) was N-hydroxylated at approximately 1/3 the rate of 4-BA, yielding 100 nmoles N-OH-2-NA/nmole P-450/10 min. N-Hydroxylation of 1-naphthylamine (1-NA) was not detected. These results correlate almost exactly with the carcinogenic activity of these amines. They strongly suggest that it is the amine itself which is the active urinary carcinogen, and that the critical carcinogenic activation takes place within the bladder mucosal cells themselves, not in the liver as was previously believed. Further support for our new hypothesis was obtained from mutagenicity assays using bladder mucosal S-9 activation of the above 3 aromatic amines in *S. typhimurium* strain TA 98. Approximately two-three times more revertants were produced with 4-BA than with 2-NA. No significant increase over background reversion was found with 1-NA. In recent studies, microsomes isolated from dog bladder mucosa were also demonstrated to contain cytochrome P-450 and mediate the N-hydroxylation of 4-BA. The rate was significantly higher than with dog liver microsomes. In addition, evidence for bladder microsomal N-hydroxylation of the bladder carcinogen 4,4-methylene-bis-(2-chloroaniline) (MBOCA) has been obtained. Mass spectrometric analysis of a major microsomal metabolite gave a fragmentation pattern consistent with the structure of the mono-N-hydroxy derivative of MBOCA.

Plans: Our future plans include: investigation of the N-oxidized metabolites of MBOCA; investigation of the possibility that there are two N-hydroxylases, one for acetamides and another for amines; make a comparison of the N-hydroxylating ability of the liver and bladder of rats, dogs, and humans; and confirm our *in vitro* observations with intact mammalian tissues such as cultured bladder explants.

Publications:

Radomski, J.L., Deichmann, Wm.B., Altman, N.H. and Radomski, T.: Failure of pure 1-naphthylamine to induce bladder tumors in dogs. *Cancer Res.* 40: 3537-3539, 1980.

Hirao, Y., Miyata, Y., Hearn, Wm.L., Radomski, J.L., and Oyasu, R.: Development of sarcomas in heterotopically transplanted rat urinary bladder unit exposed

Program Director: William E. Straile, Ph.D.

to glucuronic acid conjugate of N-hydroxy-4-aminobiphenyl. Cancer Letters
11:309-313, 1981.

National Prostatic Cancer Project
Cooperative Clinical Trials

From 06/01/73 to 02/28/82

FY 81: \$897,936

Objectives: The objective of the cooperative clinical trials program of the National Prostatic Cancer Project (NPCP) is to determine the efficacy of hormonal and non-hormonal chemotherapeutic agents, singly and in combination, in the treatment of patients with different stages of adenocarcinoma of the prostate. Patients with different stages of prostatic cancer are randomly assigned in appropriate clinical trials to the designated treatment. If remission or clinical benefit ensues, therapy is continued indefinitely. Patients with progressive disease are crossed over to alternative treatment. All patients are monitored until death. The ultimate goal is to improve survival in advanced disease and to cure patients with localized disease.

<u>Grant #</u>	<u>Start</u>	<u>End</u>	<u>FY 81</u>	<u>PI/Organization</u>
15108	06/01/73	02/28/82	\$ 99,201	Stefan Loening, M.D./ University of Iowa
15284	06/01/73	02/28/82	\$ 66,870	George Prout, M.D./ Massachusetts General Hospital
15407	06/01/73	02/28/82	\$ 92,633	William Scott, M.D./ Johns Hopkins University
15421	06/15/73	02/28/82	\$183,411	Robert Gibbons, M.D./ Virginia Mason Research Center
20618	06/30/76	02/28/82	\$ 32,156	Mark Soloway, M.D./ University of Tennessee
21438	12/01/76	02/28/82	\$140,613	Joseph Schmidt, M.D./ University of California San Diego
22387	02/01/78	02/28/82	\$ 77,975	Stuart Bergman, M.D./ Tulane University
22508	04/01/78	02/28/82	\$ 81,089	James Pierce, M.D./ Wayne State University
28500	05/01/80	02/28/82	\$ 76,742	Peter Scardino, M.D./ Baylor University
28794	05/01/80	02/28/82	\$ 47,246	Sunmolu Beckley, M.D./ Roswell Park Memorial Institute

Accomplishments: Since its inception in 1973, the clinical trials program of the NPCP has completed six trials for patients with advanced, hormone refractory prostatic cancer, and one for patients with newly diagnosed advanced disease. The current program consists of six active studies comprised of

Program Director: Andrew Chiarodo, Ph.D.

(a) two protocols for advanced, hormone refractory disease, one of which is for previously irradiated patients, (b) two protocols for advanced disease patients who have not become hormone refractory, one of which is for newly diagnosed patients and the other is for patients that are stable to estrogen or orchiectomy, and (c) two adjuvant protocols in which patients may receive long term chemotherapy following definitive surgery or radiotherapy. This program of six clinical trials provides a potential treatment regimen for patients with all but very early stages (A₁B₁) of prostate cancer. At present, ten funded and three provisional treatment centers are participating in this program and over 1800 patients have been entered. These trials have demonstrated that patients who have become failures to hormonal therapy may still benefit from systemic therapy in the form of single or combination antineoplastic agents. Therefore, some of the current trials have been designed to examine which of the agents is most effective when used singly or in combination with other antineoplastic agents or hormonal agents in patients with a smaller tumor burden including newly diagnosed stage D disease, hormonally stabilized stage D disease, or localized disease as long term adjuvant to definitive surgery or radiotherapy. Based on objective response criteria, 5-fluorouracil, cytoxan, streptozotocin, estracyt, and DTIC have shown good activity with manageable side effects, and responders have experienced markedly increased survival over non-responders. Histological material from patients in these trials is being used to study grading systems and related factors; serum samples routinely collected from these patients have been used in tumor marker studies.

Plans: The clinical trials of the NPCP will continue to investigate hormonal and non-hormonal chemotherapy, singly and in combination to determine the most efficacious treatment against both metastatic and localized prostatic cancer. Two trials in patients with advanced disease will be replaced later this year (Fall 1981). Histologic material and serum samples will continue to provide the basis for work in grading and tumor markers. The growing data bank will be used to study factors influencing treatment and disease.

Publications:

Kirdani, R.Y., Karr, J.P., Murphy, G.P. and Sandberg, A.A.: Prostate Cancer. Plasma Concentrations of Estramustine Phosphate and its Metabolites. New York State J. Med., 80:1390-1393, 1980.

Lee, C.L., Chu, T.M., Wajzman, L.Z., Slack, N.H. and Murphy, G.P.: Value of New Fluorescent Immunoassay for Human Prostatic Acid Phosphatase in Prostatic Cancer. Urology, 15:338-341. 1980.

Lee, C.L., Killian, C.S., Murphy, G.P. and Chu, T.M.: A Solidphase Immuno-adsorbent Assay for Serum Prostatic Acid Phosphatase. Clin. Chim. Acta, 101:209-216, 1980.

Murphy, G.P. and Slack, N.H.: The questionable Use of Hormone Therapy in Advanced Carcinoma of the Prostate. Urologic Clinics of North America, 7:631-638. 1980.

Murphy, G.P. and Slack, N.H.: Response Criteria for the Prostate of the USA National Prostatic Cancer Project. The Prostate, 1:375-382. 1980.

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Slack, N.H., Karr, J.P., Chu, T.M., Murphy, G.P. and Investigators in the National Prostatic Cancer Project: An Assessment of Bone Scans for Monitoring Osseous Metastases in Patients Being Treated for Prostate Carcinoma. The Prostate, 1:259-270. 1980.

Slack, N.H., Mittelman, A., Brady, M.F., Murphy, G.P. and Investigators in the National Prostatic Cancer Project: The Importance of the Stable Category for Chemotherapy Treated Patients with Advanced and Relapsing Prostate Cancer. Cancer, 46:2393-2402. 1980.

Slack, N.H., Murphy, G.P. and Participants in the National Prostatic Cancer Project: Overview of Chemotherapy Programs of the NPCP. The Prostate, 1:367-373. 1980.

Gaeta, J.: Glandular Profiles and Cellular Patterns in Prostate Cancer Grading. National Prostatic Cancer Project System. Urology, 17:33-37. 1981.

Slack, N.H., Chu, T.M., Wajsman, L.Z. and Murphy, G.P.: Carcinoplacental Isoenzyme (Regan) in Carcinoma of the Prostate. Cancer, 47:146-151. 1981.

Soloway, M.S., deKernion, J.B., Gibbons, R.P., Johnson, D.E., Loening, S.A., Pontes, E.J., Prout, G.R., Jr., Schmidt, J.D., Scott, W.W., Chu, T.M., Gaeta, J.F., Slack, N.H. and Murphy, G.P.: Comparison of Estracyt and Vincristine Alone or in Combination for Patients with Advanced, Hormone Refractory, Previously Irradiated Carcinoma of the Prostate. J. Urol., 125-667. 1981

Killian, C.S., Vargas, F.P., Pontes, E.J., Beckley, S., Slack, N.H., Murphy, G.P. and Chu, T.M.: The Use of Serum Isoenzymes of Alkaline and Acid Phosphatase as Possible Quantitative Markers of Tumor Load in Prostate Cancer. The Prostate, In Press.

Loening, S.A., Scott, W.W., deKernion, J., Gibbons, R.P., Johnson, D.E., Pontes, E.J., Prout, G.R., Jr., Schmidt, J.D., Soloway, M.S., Chu, T.M., Gaeta, J.F., Slack, N.H. and Murphy, G.P.: A Comparison of Hydroxyurea, MethylCCNU and Cyclophosphamide in Patients with Advanced Carcinoma of the Prostate. J. Urol.,

Schmidt, J.D., Slack, N.H., Chu, T.M. and Murphy, G.P.: Placentalike Isoenzyme of Alkaline Phosphatase in Patients with Advanced Prostatic Cancer. J. Urol., In Press.

Grant 15126: Biological Markers in Treatment of Prostate Cancer

From 06/01/73 to 05/30/82

FY 81: \$48,939

Dr. T. Ming Chu, Department of Diagnostic Immunology Research and Biochemistry,
Roswell Park Memorial Institute, 666 Elm Street, Buffalo, N.Y. 14263

Objectives: The objective of this project is to provide a core support for the Treatment Sub-Group, National Prostatic Cancer Project. Specifically, a series of biological markers, i.e., serum acid phosphatase, prostate specific acid phosphatase, alkaline phosphatase and isoenzyme (bone, liver, "Regan" or placenta), as well as erythrocyte polyamines (putrescine, spermidine, spermine) are to be measured by specific immunochemical and biochemical assays. These data are to be used for clinicopathological correlation. Additionally, a serum bank of prostate cancer has been established as a biological core resource. Furthermore, biological markers which may be useful for prostate cancer are to be included for this study whenever they are identified and available. To this end, the following goals have been investigated: Further evaluation of PAP as a means in early detection of disease recurrence in protocols 500, 900 and 1000 patients; study of serial erythrocytic polyamines in a multiple-marker system, i.e., for prostate cancer along with PAP and alkaline phosphatase isoenzymes; further development of an automated HPLC system for quantitation of alkaline phosphatase isoenzymes; evaluation of the new prostate-specific antigen as a marker for early detection of disease recurrence in curative localized prostate cancer and for monitoring response of treatment in advanced prostate cancer; and finally, additional collection of serum from early prostate cancer for Serum Bank.

Accomplishments: The following major accomplishments have been achieved during the past year: A clinicopathological evaluation of the isoenzyme of serum alkaline phosphatase and tumor response in advanced prostate cancer has shown that these isoenzymes may be quantitative and effective biochemical markers of bone and liver metastasis and can serve as an adjuvant means for monitoring the efficacy of therapy. Serum prostate-specific acid phosphatase, as measured by immunochemical assays (such as quantitative counterimmunoelectrophoresis), can be sensitive marker in monitoring prostate cancer, particularly when regular acid phosphatase level was slightly elevated or in a normal range. The newly developed enzyme-linked immunosorbent assay for serum prostatic acid phosphatase, which measures only the prostatic acid phosphatase protein and requires no isotope has provided an alternative means for RIA. This assay is different from our previously reported several immunoassays (CIEP, SPIF, SPIA), which measure both prostatic acid phosphatase protein and hydrolytic activity. Some serum specimens from early stage of prostate cancer have been included in the NPCP Serum Bank, although the number is still limited. This new addition makes this core resource a more complete facility.

Plans: As indicated, one of the objectives of this research project is to evaluate new biological marker for prostate cancer. For the coming year, the newly identified prostate antigen is to be included in the study, particularly, a combination test of prostatic acid phosphatase and prostate cancer will be clinically evaluated. Quantitation of polyamines in erythrocytes by our developed high pressure liquid chromatography also will be used as an additional marker. Further collection of serum specimens from early prostate cancer is to continue.

Program Director: Andrew Chiarodo, Ph.D.

Publications:

Lee, C.L., Chu, T.M., Wajzman, Z., Slack, N.H., Murphy, G.P.: Value of a New Fluorescent Immunoassay for Human Prostatic Acid Phosphatase in Prostate Cancer. Urol. 25:338-341. 1980.

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Killian, C.S., Vargas, F.P., Pontes, E.J., Beckley, S., Slack, N.H., Murphy, G.P., Chu, T.M.: The Use of Serum Isoenzymes of Alkaline and Acid Phosphatase as Possible Quantitative Markers of Tumor Load in Prostate Cancer. The Prostate (In Press).

Slack, N.H., Karr, J.P., Chu, T.M., Murphy, G.P. and Investigators in the National Prostatic Cancer Project: An Assessment of Bone Scans for Monitoring Osseous Metastases in Patients Being Treated for Prostate Carcinoma. The Prostate 1:259-270. 1980.

Grant 15292: Detection and Isolation of Human Bladder Neoantigens

From 12/01/73 to 11/30/80

FY 81: 0 (Ann. \$65,251)

David F. Paulson, M.D., Duke University Medical Center, Durham, North Carolina

Objectives: The purpose of these studies is to define those antigens that are unique to or are associated with bladder carcinoma and to raise monoclonal antibodies to such antigens. Monoclonal antibodies will be tested for their ability to specifically target bladder carcinoma tissue in vivo using the nude mouse model system. Monoclonal antibodies will be raised against isolated antigen shown to be bladder-specific, tumor-associated, or bladder tumor specific on the basis of the bladder cancer patient's humoral antibody recognition of bladder antigens. Since some bladder antigens may be of weak immunogenicity in the bladder cancer host, mouse monoclonal antibodies will also be raised using whole cell immunization procedures.

Accomplishments: A dual approach of defining antigens in a host-tumor context and raising monoclonal antibodies to antigens with demonstrated tumor-associated characteristics has been successful for prostatic carcinoma. Prostatic cancer patient IgG was immobilized on Sepharose-protein A and exposed to extrinsically labeled prostatic tumor extracts. Radiolabeled antigens specifically bound to the immunoabsorbent were quantitatively eluted in the form of immune complexes and characterized with regard to molecular weight. Rigorous sequential adsorption analyses of prostatic carcinoma patient serum, under conditions whereby antigens recognized after each sequential adsorption step have been physicochemically characterized, have allowed a serological definition of candidate prostate tumor antigens of 54- and 48 Kd subunit MW.

Monoclonal antibodies have been raised against cultured prostatic carcinoma cells, against primary prostatic carcinoma tissue extracts, and against sub-fractions of tissue extracts. The monoclonal antibodies generated have been characterized with regard to isotype, MW of antigen recognized, differential target cell binding using a panel of target cells derived from colon, bladder, breast, and prostatic carcinomas, and on the basis of differential cultured prostatic cell carcinoma binding following adsorption with various normal and malignant tissue extracts.

Plans: The long-term goal of the research is to develop a panel of monoclonal antibodies with immunotherapeutic or chemotherapeutic potential.

Program Director: William E. Straile, Ph.D.

From: 06/15/73 to 05/31/82

FY 81: \$171,096 (est).

Dr. Emerich S. Fiala, American Health Foundation, Naylor Dana Institute for Disease Prevention, Dana Road, Valhalla, NY 10393

Objectives: While the involvement of chemical agents is strongly suspected, the etiology of human large bowel cancer is still unknown. Animal models, if thoroughly understood and defined, could be of utility in determining factors which may accelerate, prevent, or delay the development of colon cancers. The aims of this program are to investigate: 1) the metabolism of colon-specific hydrazo and azoxy carcinogens in order to elucidate the mechanisms of their organotropism and carcinogenicity; 2) the mechanisms whereby genetic, chemical, and dietary factors may influence the metabolism of these carcinogens and hence their potency; and 3) whether colon-specific carcinogens can be formed endogenously, in animals or in the human.

Accomplishments: To test the hypothesis that alcohol dehydrogenase (ADH) may direct the activation and organotropism of methylazoxymethanol (MAM), we pretreated rats with pyrazole, an inhibitor of the enzyme, and studied the metabolism of MAM-¹⁴C. In pyrazole pretreated rats the metabolism of MAM-¹⁴C to ¹⁴CO₂ decreased significantly while unmetabolized MAM was increased in the urine. The inhibition was never complete regardless of the dose of pyrazole given, indicating that, while a major portion of MAM had been metabolized by ADH, spontaneous decomposition or enzymatic routes other than ADH were also functional. We examined the effects of high and low fat diets on the carcinogenicity of several colon-specific carcinogens in mouse strains with high or low susceptibility to 1,2-dimethylhydrazine. A high fat diet increased the multiplicity of colon tumors, demonstrating that diet can have a significant effect on modulating genetic susceptibility to colon carcinogenesis. We postulated that aliphatic amines could be converted to carcinogenic azoxy compounds by biological oxidizing systems. Incubation of phenylethylamine or cyclohexylamine, with rabbit liver microsomes and co-factors resulted in the formation of azoxy-2-phenylethane or azoxycyclohexane, respectively, as determined by high pressure liquid chromatography, gas chromatography and mass spectrometry. These metabolites were mutagenic in *S. typhimurium* strains TA 100 and TA 1535 with S-9 activation. This represents the first demonstration of the formation of possibly carcinogenic aliphatic azoxy compounds from the corresponding amines by a mammalian system.

Plans: The finding that aliphatic azoxy compounds can be generated from aliphatic amines by liver microsomal oxidase systems suggests that many "spontaneous" cancers, including human colon cancer, may owe their etiology to the endogenous generation of azoxy carcinogens. A likely source of substrates is the decarboxylation of amino acids to aliphatic amines by the intestinal bacteria. Because of its enormous potential importance, priority, in this program, will be given to testing this mechanism.

Publications:

Fiala, E.S., Kohl, N.E., Hecht, S.S., Yang, J.J. and Shimada, T.: The Formation of Azoxy-2-phenylethane During the Biological Oxidation of Phenylethylamine by Rabbit Liver Microsomes. *Carcinogenesis*, 2:165-173, 1981.

Program Director: Vincent J. Cairoli, Ph.D.

From: 01/01/74 to 12/31/80

FY 81: -0- (Ann. \$61,861)

Dr. Stephen W. Barthold, Yale University School of Medicine, 375 Congress Avenue,
New Haven, CT 06510

Objectives: The primary objective of this project is to investigate the promotional relationship of colonic mucosal hyperplasia with chemical carcinogenesis. This is being approached with a mouse model system utilizing the carcinogen 1,2-dimethylhydrazine (DMH) interacting with hyperplasia induced by a variant of Citobacter freundii. Specific objectives for this year were to complete ongoing studies which were to: 1) establish that hyperplasia allows the initiation of carcinogenesis with single, subthreshold doses of DMH; 2) study the sequential morphogenesis of DMH neoplastic foci emanating from a single DMH dose; 3) study cell kinetic changes in DMH-treated background mucosa and stages of neoplasia; 4) determine if stages of DMH neoplasia are responsive to a hyperplastic stimulus; and 5) examine the ability of the colonic mucosa to repair DMH-initiated damage.

Accomplishments: Hyperplasia was shown to promote the induction of DMH focal atypia with subthreshold doses of carcinogen. Mice with hyperplasia developed significantly more DMH focal atypia than did mice without hyperplasia following a single dose of DMH (20 mg/kg). Mice with hyperplasia also developed DMH focal atypia with diminished doses of DMH (10 and 5 mg/kg), while normal mice did not. Sequential morphogenesis studies showed that focal atypia arising from a single dose of DMH are reversible and may represent a precursor lesion as seen in other tissues.

Proliferative activity of background and neoplastic colonic mucosa was examined following 5 months of weekly injections of DMH (20 mg/kg) and 1 or 4 months of rest to determine whether changes result from an acute or chronic effect of DMH and whether differences exist between stages of neoplasia. To determine whether neoplasia is responsive to a proliferative stimulus, DMH-treated mice were inoculated with C. freundii. The labeling index (LI) and the proliferative zone and crypt heights increased, but the mitotic index (MI) decreased. There was a positive linear correlation between advancing tumor grade and increasing tumor LI and MI. Background LI, even when elevated by C. freundii inoculation, had no effect upon tumor LI. MI diminished in background and neoplastic mucosa following prolonged rest and increased in both following C. freundii inoculation. These studies show that DMH causes long-term changes in background mucosa apart from a reparative response to cytotoxicity. As tumors progress, LI and MI increase, suggesting a multistage process of evolution. Studies designed to examine the ability of colonic mucosa to repair DMH-initiated damage are partially completed.

Plans: It is planned to complete the objectives as stated above.

Publications:

Barthold, S. and Beck, D.: Modification of Early Dimethylhydrazine Carcinogenesis by Colonic Mucosal Hyperplasia. Cancer Res., 40:4451-4455, 1980.

Barthold, S.: The Microbiology of Transmissible Murine Colonic Hyperplasia. Lab. An. Sci., 30:167-173, 1980.

Program Director: Vincent J. Cairoli, Ph.D.

Grant 15416: Chemotherapeutic Agents and Prostatic DNA Synthesis

From 06/15/73 to 02/28/82

FY 81: \$157,465

Dr. Donald S. Coffey, Department Pharmacology and Experimental Therapeutics,
Johns Hopkins University, 725 North Wolfe Street, Baltimore, Maryland 21205

Objectives: The purpose of this grant is to characterize and study an animal model for prostatic cancer which may have properties which would be important in understanding the tumor biology of prostatic cancer. It is the purpose of this study to elucidate the advantages and limitations of animal models in this endeavor.

Accomplishments: This grant has supported the first full characterization of the Dunning R-3327 transplantable rat prostatic adenocarcinoma model. The system was characterized with respect to its growth properties, histochemistry, biochemical parameters, and pathology. The discoveries which have been forthcoming from this study include: (a) The first clear example of tumor heterogeneity of the mechanism for explaining the development of hormone resistance in prostate cancer. Following castration or estrogen therapy, the tumor involutes and then relapses to a hormone-insensitive state. It was clearly demonstrated that this was due to selection of a subclone of cells that were hormone-insensitive at the time the treatment was initiated. It now appears that a similar situation may exist in human prostate cancer and this should have dramatic impact on our consideration of how we approach or prevent the hormone-insensitive state in humans. (b) The development of tumor cell heterogeneity in the progression of tumors has been under study and we are obtaining insight into how this may develop. (c) The first study trying to biochemically distinguish hormone-sensitive from hormone-insensitive tissues in prostate cancer was accomplished in this model. It was possible to develop an enzymatic approach which gave a profile that allowed the clear selection of these two types of tumors. This could not be accomplished with receptor studies but requires enzymatic information. (d) We have developed a subline of prostatic adenocarcinoma that has the ability to metastasize. The Dunning tumor was always criticized for its low rate of distant metastasis. We have obtained a tumor system that does metastasize and we have shown some specificity for its route and organ specificity. This is shedding new light on our studies of metastasis in these models. (e) We have been able to grow the Dunning tumor on the chorioallantoic membrane of the chicken and this may serve as a model for studying metastasis.

Plans: Our plans for the near future are to continue our studies of the mechanism of metastasis, and to study how progression occurs within this tumor line. We believe that full understanding of the biological principles of prostate cancer in this animal model will be very enlightening to elucidate some important questions considered in the human disease.

Publications:

Isaacs, J.T. and Coffey, D.S. Androgenic Control of Prostatic Growth: Regulation of Steroid Levels. In, Prostate Cancer. A Series of Workshops on the Biology of Human Cancer, Report No. 9 (Coffey, D.S. and Isaacs, J.T., Eds.). International Union Against Cancer, Geneva. pp. 112-122. 1979.

Program Director: Andrew Chiarodo, Ph.D.

Isaacs, J.T., and Coffey, D.S. Spontaneous Animal Models for Prostatic Cancer. In Prostate Cancer. A Series of Workshops on the Biology of Human Cancer. Report No. 9 (Coffey, D.S. and Isaacs, J.T., Eds.). International Union Against Cancer, Geneva. pp. 195-217. 1979.

Coffey, D.S. and Isaacs, J.T. Experimental Concepts in the Design of New Treatments for Human Prostatic Cancer. In Prostate Cancer. A Series of Workshops on the Biology of Human Cancer, Report No. 9 (Coffey, D.S. and Isaacs, J.T., Eds.). International Union Against Cancer, Geneva. pp. 233-259. 1979.

J.T. Isaacs, G.W. Yu and D.S. Coffey. The Characterization of a Newly Identified, Highly Metastatic Variety of the Dunning R-3327 Prostatic Adenocarcinoma System: The Mat-LyLu Tumor. Invest. Urol. (In Press).

D.S. Coffey and J.T. Isaacs. The Control of Prostate Growth. Urology XVII, Number 3. pp. 17. March, 1981.

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Grant CA 15429: Detection of Early Colon Cancer

From: 01/01/74 to 03/31/82

FY 81: \$431,838

Dr. Sidney J. Winawer, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue,
New York, NY 10021

Objectives: This program is testing the hypothesis that screening for fecal occult blood in a standard-risk, mainly asymptomatic population is feasible and can detect colorectal cancer at an early stage. Our objective is to determine the value of both fecal occult blood testing and proctosigmoidoscopy as screening techniques within the framework of the health care system. Quality control of fecal occult blood testing is being monitored and will provide a more meaningful assessment of the results of screening with fecal occult blood tests. Results of this study could form the basis for screening asymptomatic people at average risk in order to increase the percentage of patients coming for surgery with localized cancers, resulting in improved long-term survival.

Accomplishments: A patient population of almost 22,000 people has been enrolled, examined, evaluated for risk factors, and screened for colorectal cancer, either with proctosigmoidoscopy alone or in combination with Hemoccult slides. A substantial number of these patients (approximately 50%) have returned voluntarily for at least one repeat examination. The program's continuing activity is reflected in the following statistics: total number of examinations 44,358; number of proctosigmoidoscopies 41,710; and total number of Hemoccult slide tests 22,767.

Data analyses also include: rates of positivity and predictive value of various types of Hemoccult slides; factors influencing predictive value such as age, number of positive slides, and number of slides prepared; relative sensitivity of rigid and flexible sigmoidoscopy; relative sensitivity of various diagnostic techniques, including double-contrast barium enema, and colonoscopy; evaluation of brush cytology, target biopsy, and lavage cytology; comparison of Hemoccult and proctoscopy findings in the rectosigmoid area; size, staging, and location of detected adenomas and cancers; rates of false-negative and false-positives in the rectosigmoid area; detailed family and patient histories of cancer and colon disorders; comparison of patient and physician reported symptomatology; depth, ease, and findings of proctoscopic and digital examinations; analyses of factors related to patient compliance with fecal occult blood testing; comparison of annual and initial patient profiles in terms of demographics, history, symptoms, and yield of findings; the establishment of a reference laboratory for quality control of fecal occult blood testing; patient risk of screening, diagnosis, and treatment; and evaluation of tumor markers including carcinoembryonic antigen in lavage fluid and cell proliferative studies of biopsies and cells obtained by lavage.

Plans: Beyond demonstrating the feasibility of screening, the value of fecal occult testing must be ascertained through the long-term effort of accumulating survival and mortality statistics on the study and control groups.

Publications:

Winawer, S.F., Andrews M., Flehinger, B., Sherlock, P., Schottenfeld, D., and Miller, D.G.: Progress Report on Controlled Trial of Fecal Occult Blood Testing for the Detection of Colorectal Neoplasia. Cancer, 54:2959-2964, 1980.

Program Director: Vincent J. Cairolì, Ph.D.

Grant 15436: Test Systems for Drugs Against Prostatic Cancer

From 10/01/73 to 11/30/82

FY 81: \$114,986

Dr. Avery A. Sandberg, Department of Medicine C, New York State Department of Health, Empire State Plaza, Albany, N.Y. 12237 and Health Research, Inc., Roswell Park Division, Buffalo, N.Y. 14263

Objectives: The major aims of the project have been the development and application of various test systems useful in the testing of drugs potentially useful in prostatic cancer. The development of such approaches has placed emphasis on in vitro and in vivo model systems with particular attention to the utilization of human material from individual patients, so that specificity can be obtained for the treatment in each case. The development of these systems has taken advantage of certain unique features of the prostate (enzymatic, steroidal, hormonal) so that the effects of drugs could be measured in terms of events unique to prostatic tissue. During the last few years emphasis has been placed on in vitro systems for testing drugs with the following advantages: (1) human tumor tissue can be used, (2) only small amounts of tissue are required, (3) the time of testing is considerably shortened and, most importantly, (4) a number of agents can be tested simultaneously.

Accomplishments: During the past years a number of systems which have been used for the testing of drugs have been established in our laboratory. The initial systems relied on the effects of various drugs and agents on 5 α -reductase and arginase activities in animal prostates, both in vitro and in vivo, and on the human prostate in vitro. Other test systems have utilized as an index of drug activity the effects on the deposition of various steroids in the prostate after injection into animals, the activity being related to the presence of various specific receptors. The latter approach has also led to our undertaking a number of studies on receptor parameters, both androgenic and estrogenic, as they relate to the effects of various agents. During the years, a number of drugs which have been found to be active in these systems have been used by the NPCP clinically.

During the last few years we have devoted considerable effort towards establishing organ culture methods for studying the effects of various drugs on human prostatic tissue obtained from individual patients. These effects relate to DNA synthesis, 5 α -reductase and arginase activities, metabolism of testosterone and, more recently, effects on chromatin and chromosomes.

Plans: Our future plans are related to expanding the range of test systems by including two important areas: relation of chromosome changes to the histology and behavior of prostatic tumors and utilization of sister chromatid exchange (SCE) as a test system for drugs potentially useful in prostatic cancer. The former approach will hopefully yield information on the possibility of specific karyotypic changes being present in prostatic cancer, potentially reflecting receptor, enzymatic and biologic status of such tumors. This indeed would be an important advance, for it would afford an additional means of classifying prostatic tumors. The use of SCE as a test system for potential drugs is related to the fact that this appears to be the most sensitive system for testing mutagens and/or carcinogens available at present. What we hope to do is to utilize in vitro systems (short term culture of human prostatic cancer cells, organ

Program Director: Andrew Chiarodo, Ph.D.

culture of human and animal prostatic cancers and established prostatic cancer cell liver of human origin) and study the effects of various drugs on the SCE level.

Publications:

Karr, J.P., Kirdani, R.Y., Murphy, G.P., and Sandberg, A.A.: Androgen Binding in the Baboon Prostate. Arch. Androl. 2: 123-128. 1979.

Karr, J.P., and Sandberg, A.A.: Steroid Receptors and Prostatic Cancer. In: Prostatic Cancer, Ed. G.P. Murphy, P.S.G. Publishing Co., Littleton, Mass., pp. 49-74. 1979.

Muntzing, J., Kirdani, R.Y., Murphy, G.P. and Sandberg, A.A.: A Rat Prostatic Adenocarcinoma as a Model for the Human Disease. Invest. Urol. 17: 37-41. 1979.

Karr, J.P., Wajzman, Z., Madajewicz, S., Kirdani, R.Y., Murphy, G.P. and Sandberg, A.A.: Steroid Hormone Receptors in the Prostate. J. Urol. 122: 170-175. 1979.

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Karr, J.P., Kirdani, R.Y., Murphy, G.P. and Sandberg, A.A.: The Baboon Prostate as a Model for Steroid Hormone Receptors in the Human Gland. In: Hormone Receptors and Prostatic Cancer, Eds. G.P. Murphy and A.A. Sandberg, Alan R. Liss, Inc., New York, 1979, pp. 165-179.

Kirdani, R.Y., Murphy, G.P., Priore, R.L. and Sandberg, A.A.: Systematization of Scatchard or Lineweaver Burk Plot. Linearization: Application to Receptor Analysis. In: Prostate Cancer in Hormone Receptors, Publisher, Alan R. Liss, 1978. (In Press), 150 Fifth Avenue, New York, N.Y. 10011, pp. 145-164. 1979.

Catane, R., Mittelman, A., Murphy, G.P. and Sandberg, A.A.: Effects of Testosterone on Estracyt Localization in Rat Prostate. Oncology 37: 357-359. 1980.

Sandberg, A.A., Karr, J.P., and Muntzing, J.: Animal Models for Diseases of the Human Prostate: The Prostates of Dog, Baboon and Rat. In: Male Accessory Sex Glands: Biology and Pathology, Ed. E. Spring-Mills and Hafez, Elsevier North-Holland Biomedical Press, Amsterdam, 32: 56 5-608. 1980.

Sandberg, A.A. and Karr, J.P.: Hormonal Receptors in Human Neoplasia. In: International Review of Surgical Oncology 3: 311-350. 1980.

Kirdani, R.Y., Plym Forshell, Y., Karr, J.P., Murphy, G.P. and Sandberg, A.A.: Plasma Concentrations of Estracyt and Its Metabolites in Patients with Prostate Cancer. N.Y. State J. Med. 80: 1390-1393. 1980.

Corrales, J.J., Hisaeter, P.A., Kadohama, N., Murphy, G.P. and Sandberg, A.A.: A Model for Studies on the Response of the Ventral Prostate to Estrogens. Acta Endocrinol, (In Press).

Horoszewicz, J.S., Leong, S.S., Ming Chu, T., Wajzman, Z.L., Friedman, M., Papsidero, L., Kim, U., Chai, L.S., Kakati, S., Arya, S.K. and Sandberg, A.A.: The LNCaP Cell Line - A New Model for Studies on Human Prostatic Carcinoma. In: Models for Prostate Cancer, Alan R. Liss, Inc., New York, N.Y., pp. 115-132. 1980.

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Karr, J.P., Wajzman, Z., Kirdani, R.Y., Murphy G.P. and Sandberg, A.A.: Effects of Diethylstilbestrol and Estramustine and Phosphate on Serum Sex Hormone Binding Globulin and Testosterone Levels in Prostate Cancer Patients. J. Urol. 124: 232-236. 1980.

Sandberg, A.A.: Chromosomes as Markers in Human Cancer. In: International Advances in Surgical Oncology, Vol. 4, pp. 311-336, Ed. Murphy, G.P., Alan R. Liss, Inc., New York. 1980.

Sandberg, A.A.: The Fate and Biochemical Effects of Estracyt in the Human and Baboon. In: Cytotoxic Estrogens in Hormone Receptive Tumors. (Eds.) J. Raus, H. Martens and G. Leclercq, Academic Press, Inc., London, pp. 219-243. 1980.

Sandberg, A.A.: Rationale and Practice of Testing Chemotherapeutic Agents for Prostate Cancer. Urology. (In Press).

From 10/01/73 to 11/30/82

FY 81: 124,750

Dr. T. Ming Chu, Department of Diagnostic Immunology Research and Biochemistry,
Roswell Park Memorial Institute, Buffalo, N.Y. 14263

Objectives: The overall objectives of this project are to isolate and characterize antigen markers specific for or associated with human prostate cancer. Specific immunologic reagents are then produced for development of immunodiagnostic procedures for these antigenic markers, whereby to detect prostate cancer at an early stage and to monitor efficacy of treatment. In order to achieve these objectives, the following specific aims have been emphasized: to improve a purification procedure for our newly identified human prostate antigen; to develop sensitive immunoassay for this antigen; to produce hybridoma derived monoclonal antibodies to prostate antigen and last, but not least, to continue our search for a prostate tumor-specific antigen(s).

Accomplishments: Our major accomplishment has been with the work on the newly identified human prostate specific antigen. This antigen has been shown to be distinct biochemically and immunologically from prostatic acid phosphatase. By immunoprecipitation and immunohistochemical techniques, prostate antigen has been shown to be a tissue specific antigen of human prostate. It is a prostatic epithelial marker protein. Specific antiserum has been produced in large quantity. Circulating prostate antigen in patients with prostate cancer has been isolated and shown to be immunologically identical and biochemically similar to that of prostate tissue. Further, a sensitive and specific assay technique has been developed. With all these accomplishments, it is now possible to apply the antiPA antiserum in the differential diagnosis of prostate cancer by immunohistochemical technique with tissue sections (e.g., regular formalin-fixed, paraffin-embedded tissue preparation) in the pathology laboratory. By means of the simple and sensitive enzyme-linked immunosorbent assay, quantitation of the circulating level of this antigen can be achieved, which potentially provides an additional means for diagnosis of prostate cancer, as well as for monitoring efficacy of treatment. Another possible application is the use of specific antiPA antibodies in in vivo radioimmunodetection of prostate cancer, particularly the micro-metastasis which is so critical in staging and treatment. Immune-specific chemotherapy also is a potential area where much work now can be initiated with availability of the antiserum reagent. Furthermore, physiology of the prostate can be studied with the aid of this new marker for prostate gland epithelium. In summary, much significant progress can be expected in our knowledge of and fight against prostate cancer, as well as in our study of physiology and pathology of the prostate, from the investigations of this new prostate antigen.

Plans: Many important investigations on this project are yet to be completed, although significant accomplishments have been achieved. Additional biochemical, chemical, physical and immunological characterizations of prostate antigen are underway. Isomeric forms of prostate antigen are to be isolated and characterized. Clinically, evaluation of our sensitive immunoassay in early detection of disease recurrence and in monitoring efficacy of treatment is a very important study. Also, the use of immunologic reagents of prostate

Program Director: Andrew Chiarodo, Ph.D.

antigen in in vitro and in vivo radioimmuno-localization of prostate cancer is a natural extension of this work.

Publications:

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From 12/01/73 to 11/30/82

FY 81: \$184,594

Dr. Theodore I. Malinin, Department of Surgery R-12, University of Miami,
School of Medicine, P.O. Box 016960, Miami, Florida 33101

Objectives: The patterns of changes in a variety of biological parameters in normal and neoplastic human prostate gland tissues are the subject of numerous scientific investigations conducted under the auspices of the National Prostatic Cancer Project. The objective of the present endeavor is to provide the needed materials for these investigations, to characterize this material and to initiate, study and distribute cell cultures obtained from benign and malignant tumors of prostate glands. The rationale is that primary cell cultures from normal and neoplastic human prostate glands are best suited for the study of cellular aberrations inherent to human prostate cancer. These cultures are not easy to prepare, nor do they behave uniformly. This study has established patterns of growth of cells from normal prostate glands and glands with benign and malignant tumors. Surprisingly, little difference was observed between the growth of cells from adenomatous vs. carcinomatous glands. Techniques for initiating cultures from these glands have been developed and described.

Accomplishments: During the year 1980, prostate glands were collected from 157 patients. Of these, 98 were normal, 34 were with BPH and 25 with carcinoma. These were subdivided, and 496 tissue samples and cell cultures were sent to individual investigators. Tissue explants were placed in culture from 36 prostate glands. Of these, 33 produced cell growth. The thrust of the study will be approximately the same during 1981 as judged from the first three months of the year. The past achievements of this program will include the demonstration of feasibility of initiating large numbers of primary cultures of prostate cells from explants; lack of uniform success with enzymatic dispersion, particularly with pronase, of prostate gland cells; cryopreservation of solid pieces of tissue and prostate cells; characterization by light and electron-microscopy of neoplastic and normal cells, and the establishment of a functioning prostate tissue and cells collection center and a repository.

Plans: It is planned to continue the operation of the Prostate Cancer Tissue Collection Center, and the development of a comprehensive program of supplying the National Prostatic Cancer Project Investigators with tissues and cells from human prostate glands needed for their studies. To this end, studies in characterization of material provided by the Center will be continued. Collection and addition of the animal transplantable tumor material to the frozen repository will be completed.

Publications:

Malinin, T.I., Claflin, A.J., Block, N.L. and Brown, A.L.: Establishment of Primary Cell Cultures from Normal and Neoplastic Human Prostate Gland Tissue. Progress in Clinical and Biol. Res. (Models for Prostate Cancer, G.P. Murphy, Ed.): 37. 161-180. 1980.

Program Director: Andrew Chiarodo, Ph.D.

Malinin, T.I. and Claflin, A.J.: The Miami Cell Line (UMS-1541). Ibid: pp. 111-114.

Claflin, A.J. and Malinin, T.I.: Preparation of Human Monolayer Cell Cultures from Frozen Tissue. Tiss. Cult. Assoc. Man. 5 :1095-1098. 1979.

Claflin, A.J., Pollack, A., Block, N.L., Irvin, G.L. and Malinin, T.I.: Production of Tumors with Diploid and Aneuploid Cells by Predominantly Displod Culture Cells. Fed. Proc. 40:783, 1981.

Kozlovskis, P.L., Claflin, A.J., Gratzner, H.G., Rubin, R.W., Fletcher, M.A. and Malinin, T.I.: A Cell Line Derived from a Rat Prostate Adenocarcinoma. Fed. Proc. 40:784. 1981.

Evaluation and Management of Patients with Bladder Cancer
National Bladder Cancer Collaborative Group A

From 12/01/72 to 11/30/82

FY 81: \$1,349,362

Objectives: The goal of this collaborative clinical research project is to improve the care of patients with bladder carcinoma. This is approached through studies of different aspects of clinical management and of the biology of human bladder cancer. The protocols are designed (1) to characterize patients, their neoplasms and the fields from which the neoplasms arise, (2) to evaluate systemic chemotherapy in patients with metastatic bladder carcinoma and to evaluate systemic chemotherapy as an adjuvant to preoperative radiotherapy and cystectomy in patients with invasive bladder carcinoma, (3) to assess the efficacy of combined radiotherapy and chemotherapy in patients with inoperable, invasive bladder carcinoma, and (4) to study intravesical chemotherapy in patients with superficial bladder cancer. The knowledge gained is important in understanding the heterogeneity and progression of this disease, and will result in more effective treatment strategies for the individual with bladder cancer.

During the current reporting period, Collaborative Group A (CGA) members have entered approximately 400 patients into eight protocols.

<u>Grant #</u>	<u>Start</u>	<u>End</u>	<u>FY 81</u>	<u>PI/Organization</u>
15490	12/01/71	11/30/82	\$141,646	Gilbert Friedell, M.D./ St. Vincent Hospital
15492	12/01/71	11/30/82	\$ 72,294	Warren Koontz, M.D./ Medical College of Virginia
15933	12/01/71	11/30/82	\$ 73,376	Stefan Loening, M.D./ University of Iowa
15934	12/01/71	11/30/82	\$ 99,224	Mark Soloway, M.D./ University of Tennessee
15937	12/01/71	11/30/81	\$ 59,602	Zew Wajzman, M.D./ Roswell Park Memorial Institute
15944	12/01/71	11/30/82	\$103,020	George Prout, M.D./ Massachusetts General Hospital
16886	12/01/71	11/30/82	\$ 81,417	Malachi Flanagan, M.D./ Rush Presbyterian-St. Luke's
17466	12/01/71	11/30/82	\$119,944	George Brannen, M.D./ Virginia Mason Research Center
23078	09/01/74	11/30/82	\$297,536	Sidney Cutler, D.Sc/ Georgetown University

Program Director: William E. Straile, Ph.D.

23082	12/01/75	11/30/82	\$124,557	George Prout, M.D./ Massachusetts General Hospital
25881	04/01/78	11/30/81	\$ 59,516	Patrick Walsh, M.D./ Johns Hopkins University
25891	04/01/78	11/30/81	\$ 52,155	Joseph Schmidt, M.D./ University California San Diego
25918	04/01/78	11/30/82	\$ 65,075	Harper Pearse, M.D./ University of Oregon

Accomplishments: CGA members evaluated the efficacy of DDP and the combination of DDP + Cytoxan (CY) for the treatment of patients with metastatic bladder carcinoma. Patients were prospectively randomized to DPP, 70 mg/M², or DDP, 70 mg/M², + CY 1000mg/M². There was no significant difference between the overall response rates for the treatment (DPP-9/43, 20, 9%; DDP + CY-6/47, 12.7%). This investigation was not able to confirm the previously reported Phase II studies that had reported a high response rate for DPP in the bladder. However, there was a response rate for DDP in the bladder. There was a response in a subset of patients having residual tumor in the bladder. The response was size reduction or disappearance of visible tumor. With DDP alone, the overall response rate was 1/12 (8.3%), and with DPP = CY 8/14 (57.1%). Residual primary tumor in the bladder does respond to systemic chemotherapy and DPP + CY were more effective than DPP alone.

The Subcommittee for Superficial Bladder Cancer introduced protocols to assess (1) the ablative effects of Mitomycin C (MMC) versus ThioTepa (TTPA) in a Phase III prospective randomized study, (2) the ablative effects of MMC in patients who have previously failed TTPA therapy and (3) the prophylactic effects of single dose TTPA vs single dose plus sequential TTPA. Bristol Laboratories, Syracuse, N.Y. (13201) is supplying MMC.

CGA members assessed 4000rads adjuvant preoperative radiation therapy (XRT) followed promptly (1-28 days) by radical cystectomy in patients with invasive bladder cancer. The research monitored XRT tolerance, early postoperative complications and pathological downstaging. All patients completed the scheduled megavoltage irradiation with at most mild intestinal, urinary or hematologic toxicity. Eighty-six percent of patients completed planned radical cystectomy with a median interval between XRT and surgery of 13.6 days. No patient died postoperatively. Sixty-nine percent of patients recovered without a postoperative complication, while 18% had 1, 9% had 2 and 4% had 3 complications. Pathologic downstaging occurred in 39% - 24% to pT₀ and 15% to pT₁ or pT_{1S}. For an interval between XRT and surgery of \leq 13 days, 20% of patients were down-staged to pT₀ and 63% had no postoperative complications; for an interval $>$ 13, 30% were pT₀ and 76% had no postoperative complications. The results support selecting this regimen of adjuvant full-dose preoperative XRT to shorten the interval between diagnosis and cystectomy. This allows for pathologic downstaging, and a dose likely to sterilize unresected micrometastases.

Plans: The plan for each succeeding year is to collect and analyze data on patients with proven bladder carcinoma. The observations made provide biologic, diagnostic and therapeutic response information. As in the past,

this information is disseminated to practitioners responsible for the care of patients who may or do have bladder cancer.

Publications:

Koontz, W.W., Jr., Prout, G.R., Jr., Minnis, J.E. and Smith, W., for National Bladder Cancer Collaborative Group A: The Use of Intravesical Thio-tepa in the Management of Invasive Carcinoma of the Bladder. J. Urol., 125 (3): 307-312, 1981

Cutler, S., Heney, N.M., and Friedell, G., for National Bladder Cancer Collaborative Group A: Longitudinal Study of Patients with Bladder Cancer: Factors Associated with Disease Recurrence and Progression. In Press.
In Bonney, W.W. and Prout, G.R., Jr. (Eds.): AUA Monographs, Vol. 1: Bladder Cancer. 1981.

Friedell, G., Hawkins, I., Ahmed, S. and Schmidt, J.: Role of Urinary Tract Cytology in the Detection and Clinical Management of Bladder Cancer. In Press.
In Bonney, W.W., and Prout, G.R., Jr. (Eds.): AUA Monographs, Vol. I: Bladder Cancer. 1981.

Contract N01-CN-15513: Statistical Analysis and Quality Control (SAQC) Center
for the Centralized Cancer Patient Data System (CCPDS)

From 02/01/81 - 12/31/85

FY 81: \$723,547

Dr. Polly Feigl, Fred Hutchinson Cancer Research Center
Seattle, Washington 98104

Objectives: The Statistical Analysis and Quality Control (SAQC) Center is the coordinating center for the Centralized Cancer Patient Data System (CCPDS). The short term goal of CCPDS is to provide basic cancer patient data in standardized form for all 21 U.S. Comprehensive Cancer Centers. The long term goal is to use the data system for cooperative research. Specific objectives of SAQC are: 1) to set and monitor standards for the uniformity and quality of data acquisition; 2) to computer process 50,000 new registrations per year plus annual follow-up; 3) to produce center specific and pooled data analyses, and; 4) to serve as a focus and a resource for the conduct of multi-institutional scientific studies.

Accomplishments: As of December 31, 1980 a total of 91,486 patients had been registered. All Comprehensive Cancer Centers were submitting data except two still in the pilot data phase. Data were over 90% complete for 1977 and 1978, and 70% complete for 1979. As previously, each contributing center was visited by SAQC field staff once during the year for the purpose of formally assessing data quality. A two day training workshop for the tumor registrars from the centers was held in Seattle in October, also for the purpose of enhancing data quality. A CCPDS case-finding study was initiated at the University of Pennsylvania under subcontract. In consultation with the CCPDS advisory committees the CCPDS minimal patient dataset was streamlined. Detailed plans for the conversion of the data system from its initial version to version two were designed at SAQC and implemented at the centers. A completely new Data Acquisition Manual was prepared to accompany version two of the dataset. Routine annual reports of descriptive and survival data were issued for each center and for all centers combined. Significant progress occurred in four inter-center research studies sponsored by CCPDS: 1) data collection began for a study of secular trends in diagnosis, treatment and survival of osteogenic sarcoma; 2) pilot work began for an observational study of prognostic factors in malignant melanoma; 3) epidemiologists from eight cancer centers prepared a proposal for a case-control study of ten rare tumors, and; 4) pilot study at two centers began in the area of second primary tumors. The SAQC Center provided statistical consultation data processing and coordination for these studies.

Plans: SAQC will continue monitoring input data quality and producing standard output reports for the duration of the CCPDS. As the system matures the survival and time trend data will become increasingly valuable. However, the greater scientific potential lies in the special studies now in their preliminary stages. The new efforts of SAQC will be directed to the support of these cooperative, question-driven data projects.

Publications: Laszlo, J. and Feigl, P.: Utilization of the Centralized Cancer Patient Data System. In Proceedings of the Meeting, Progress in Cancer Control, September 29-30, 1980, Roswell Park Memorial Institute.

Project Officer: Thomas C. Dundon

Contract 15531: Data Management for Collaborative Cancer Pain Study

From 03/31/81 to 01/30/83

FY 81: \$103,153

Dr. Sandy Mackintosh, National Institute for Advanced Studies, 1133 15th Street,
N.W., Washington, D.C. 20005

Objectives: To provide data management and support services to the NCI for seven institutions participating in the collaborative study Pain Control in Cancer; to expedite and coordinate the flow of project data; to provide regular updates and analyses on study results as well as special analyses required as the study progresses; to facilitate the functions of the Data Management and Report Writing committee for the study.

Accomplishments: Within two months of award the contractors met twice with the Data Management Committee. The Text Instrument Package for the study was revised and reformatted into the final version for automation. The Coding Manual was developed and finalized.

Plans: Test cases are being coded, the data base and error routine established. Data tapes from all seven contractors representing the first 30 patients entered at each site will be received by late autumn 1981. Preliminary analyses on key study questions are being performed.

Project Officer: Donald N. Buell, M.D.

From 11/1/80 to 10/31/83

FY 81: \$235,226

Kenneth A. Wright, M.S., (Elec. Engineering Dept. MIT, Cambridge, MA)

Program Office: Suite 307, 6900 Wisconsin Avenue,

Chevy Chase, Maryland 20015

Objectives: The primary objective of the program is to ensure national uniformity of review services provided by the six Centers for Radiological Physics (CRP) which operate in assigned geographic regions under individual contracts with NCI. Additional objectives are: (1) to monitor a centralized data storage facility, and to provide NCI with the digested data; (2) to supply the Project Officer with information regarding the performance of the six Centers; (3) to evaluate the CRP program's effect on cancer control; (4) to develop avenues for technology transfer to the medical physics community; (5) to coordinate CRP inter-regional activities; and (6) to prepare integrated reports on CRP activities.

Accomplishments: The program is in its seventh year of coordinating activities of the six regional Centers for Radiological Physics - this contract is a successor to contract N01-CN-45162. The overall goal of a nationwide uniformity of physics review protocols, methods and equipment calibrations was accomplished. The Coordination Program maintains close communication with the CRPs and monitors their activities by various methods, namely: review of monthly activity reports, review of semiannual scientific reports, site visits, joint meetings with the CRP Directors, and liaison at CRP task group meetings. Monthly updates of DRCCA supported clinical facilities requiring physics reviews, as well as monthly logs of reviews completed by the CRPs were submitted to NCI. A site visit to the Northeast CRP and a joint meeting (Coordination Program - CRP Directors) were held in the last quarter of 1980. The program has reviewed proposals for CRP inter-regional activities to avert duplication of effort, conflict of interest, and conflicts with the terms of their contracts. The Coordination Staff attended meetings and workshops of the following CRP task groups: Computerized Tomography, Chest Radiography and Radiation Therapy, as well as the annual CRP intercomparison meeting held in March 1981 in Houston. A request by the Western CRP to carry out a developmental task related to CT scanning has been reviewed by the Coordination Consultants. Two examinations of the data on therapy reviews stored in the computer (Southern CRP) were conducted in this period; a print-out dated February 27, 1981, contains data from 572 on-site reviews of 385 teletherapy machines at 288 clinical facilities, 1490 mailed TLD checks of 321 machines at 225 facilities, and also on-site reviews of 392 batches of brachytherapy sources at 67 institutions. The Coordination Office provided the Project Officer with integrated reports on mammography dosimetry data (BCDDPs), CRP activities in brachytherapy, and CRP educational activities and materials. The staff has monitored the cooperation between the CRPs and the BRH on the evaluation of mammographic phantoms (NCI-BRH interagency activities). The Coordination Program sponsored, the preparation of slides for a short course of continuing educations on chest radiography.

Project Officer: Winfred F. Malone, Ph.D.

Plans: Coordination activities will be continued with an emphasis on technology transfer and education. Two site visits to CRPs are scheduled for May 1981, and a joint meeting with CRP Directors for June 1981. Attention will also be directed toward evaluating the impact of the CRPs on cancer control as it relates to patient dosimetry. - Liaison with the AAPM, ACR, BRH, NBS, and NCI will be maintained.

Contract 15546: Community Hospital Oncology Program - Borgess Medical Center

From 01/01/81 to 06/30/82

FY 81: \$136. +4

Dr. Leo Zelkowitz, Borgess Medical Center, Stryker Center, Room 419,
1521 Gull Road, Kalamazoo, Michigan 49001

Objectives: To develop a multi-disciplinary, multi-institutional program which will insure that current treatment methods, diagnostic and staging techniques and programs of rehabilitation and continuing care are available and used by health professionals caring for cancer patients.

Accomplishments: This project involves the two acute care hospitals (Borgess Medical Center and Bronson Methodist Hospital) in Kalamazoo, Michigan. A consortium committee consisting of trustees, administrators and the chief of staff from both hospitals has been formed to oversee the program and to insure its continuance. In addition, multi-disciplinary physician site committees have been established to review the current literature and write specific guidelines for the management of most neoplasms seen in the community; an interdisciplinary nursing committee has been formed to develop specific care plans for patients with cancer; and a rehabilitation and continuing care committee has been formed to develop criteria for assessing the support care needs of each patient.

Plans: Each guideline, care plan and support care criterion will be reviewed by all appropriate sections, departments and committees with each participating hospital. A formal system for implementing each of these will also be constructed and a system will be implemented to evaluate the impact of this process.

Project Officer: Dorothy R. Brodie, M.D.

Contract 15547: Community Hospital Oncology Program - California Hospital Medical Center

From 02/16/81 to 08/15/82

FY 81: \$100,250

Dr. J. F. McKernan, California Medical Center, 1414 South Hope Street,
Los Angeles, California 90015

Objectives: The major objectives of California Hospital Medical Center's (CHMC) oncology program will be to develop management guidelines for defining criteria for cancer patient care, and to plan and implement a program to encourage community cancer practices in accordance with these criteria. The extent to which current practices correspond to these recommended criteria will be assessed by the use of a data management system. The information obtained will be used to correct, modify, and improve the hospital's clinical oncology program and to document effective changes in community cancer care. Additionally, funds to ensure self-sufficiency at the termination of federal funding will be developed.

Accomplishments: With the commencement of funding on February 16, 1981 several specific tasks addressing the planning and development of this program have been accomplished. In preparation for developing patient management guidelines, committee chairmen and committee members have been selected for nursing, and for rehabilitation and continuity of care. A task force to develop a terminal care plan has also been formed with at least 14 specific tasks identified to be studied. Institutional membership in the Southern California Hospice Association has been submitted. A Cancer Screening Program offering Hospice Association has been submitted. A Cancer Screening Program offering diagnostic tests at a nominal cost to the community has been activated. An eight-week course for patient and family education being planned conjointly with the American Cancer Society (ACS), is scheduled to begin in September. Other hospitals in the Lutheran Hospital Society of Southern California have been contacted and asked to designate a person to act as a liaison with the CHMC Community Hospital Oncology Program Coordinator. The Executive Medical Board has approved medical staff participation in the objectives. All medical staff have been requested to participate in one or more of sixteen identified site committees. Through the USC Regional Activities' Program, hospital staff are involved in developing common staging forms with 26 other hospitals in the Cancer Management Network. The oncology unit is now a training site for the Macomber Oncology Nurses' Course offered through the USC Comprehensive and Cancer Center. A multi-disciplinary committee has been formed. The interdisciplinary patient care team has reorganized weekly oncology rounds from medical presentation to team discussion and has reactivated a monthly patient care conference.

Plans: By the end of the contract it is anticipated that the objectives identified in Part 1 will have been completed and a plan to implement the entire program will be ready to be activated. As part of this plan, the five other hospitals of the Lutheran Hospital Society of Southern California will also be involved in this 18-month planning period.

Project Officer: Donald N. Buell, M.D.

Contract 15548: Community Hospital Oncology Program - Christ Hospital

From 01/01/81 to 06/30/82

FY 81: \$70,400

Dr. Richard L. Meyer, Christ Hospital, 71 East Hollister Avenue, Cincinnati, Ohio 45219

Objectives: The purposes of the Tri-State Community Hospital Oncology Program include the development, implementation and maintenance of a community wide program of cancer care in community hospitals, provision of the highest achievable quality of multidisciplinary patient management, evaluation and documentation of management practices and outcomes and coordination of other patient resources to assure patients in the Tri-State area of the full spectrum of cancer resources by developing physician, nursing, and rehabilitation patient management guidelines, mechanism to make available appropriate specialized treatment protocols, cancer nursing teaching program, continuing care plan, cancer data management system, evaluation plan and self sufficiency plan.

Accomplishments: Planning activities began with the contract award January 1, 1981. The following have been accomplished; the necessary administrative and professional staff have been recruited, the physicians responsible for admitting 75% or more of the cancer patients to community hospitals were identified, the organizational structure is developed, committee activities have begun in the following areas: cancer nursing, terminal care plan, rehabilitation, and eight of the physician site committees. Various data management systems are being analyzed for selection as the CHOP data system by June 30, 1981. Proposals for the development of an evaluation plan are being considered. By September 1, 1981 the following are expected to have been accomplished: the cancer nursing guidelines should be near completion, drafts of the 12 site committees guidelines will be completed, specialty committees will be reviewing the guideline drafts, a cancer data management system will have been selected as well as an evaluation plan developed. A directory on available rehabilitation resources for cancer patients and their families will be completed. A basic plan to meet the needs of the terminally ill cancer patients will have been developed. The mechanism to make appropriate specialized protocols available will be in place.

Plans: The planning function is directed at involving as many interested individuals as possible. Plans are being made to continually seek out those physicians, nurses, and other health professionals from the member hospitals and involve them in the development of the guidelines. All of our planning activities will be directed at the objectives outlined earlier.

Project Officer: Donald N. Buell, M.D.

Contract 15549: Community Hospital Oncology Program - Hackensack Hospital

From 01/01/81 to 06/30/82

FY 81: \$79,466

Dr. Charles P. Vialotti, Hackensack Hospital, 22 Hackensack Hospital
Hackensack, New Jersey 07601

Objectives: The program is designed to develop a set of prospective management guidelines for physicians, nurses and all supportive and rehabilitative personnel. The program will address the entire spectrum of cancer care practices in our community and in doing so will create an environment in which a consistently high standard of state-of-the-art care can be delivered to all patients and their families in the participating community.

The program is also developing a responsive, accurate and significant data set and tumor registry and evaluation system. It will offer to the entire community for the first time a computerized system which will make possible the collection and retrieval of meaningful data which relates not only directly to patient care practices and outcomes but also to the process of program development and implementation and participation.

Accomplishments: There have been many accomplishments to date. The participation of other institutions within the two-county area either in the total program or in various aspects of the program is a first for this region. There has been a tremendous upsurge of community interest in the program and in the delivery of cancer care in general. The local health system agency has become very interested in our activities and we have been sharing information with them.

For the first time, physicians from the staffs of multiple institutions have been meeting together discussing treatment principles and have developed a number of patient management guidelines. Guidelines for such diseases as esophageal carcinoma, stomach carcinoma, breast carcinoma, endometrial carcinoma, ovarian carcinoma, vulvar and vaginal carcinoma, prostatic carcinoma, and colo-rectal carcinoma, have already been developed in a rough form. The Nursing Committee has developed multiple guidelines as have many of the rehabilitative committees.

Plans: Plans include finalization of the data and evaluation system. Plans also include the development of a common data set through participation with other CHOP contractors. It is planned to expand the impact of the program by invitation of additional institutions to participate in various aspects of the program.

Project Officer: Dorothy R. Brodie, M.D.

From 01/01/81 to 06/30/82

FY 81: \$71,123

Dr. Ronald F. Goldberg, Memorial Medical Center, P.O. Box 23089,
Savannah, Georgia, 31403

Objectives: Following receipt of an NCI fixed-price contract on January 1, 1981, the goal of Memorial Medical Center's Community Hospital Oncology Program has been to recruit and hire key personnel necessary to coordinate efforts in the 18-month Planning Phase. After establishing routine operations, the program is to sponsor the initiation of committees to provide information, guidance, and approvals. Through the committees, ongoing professional education will be provided. Physicians serving on committees will be responsible for writing patient management guidelines and corresponding audit criteria. In addition, a plan will be developed to evaluate the success of the CHOP's endeavors and the accuracy and usefulness of data collected.

Accomplishments: To date, all key personnel positions have been filled. These staff members have gathered data to provide a statistical base for later evaluation efforts. Furthermore, educational offerings in the form of in-services, speeches, monthly conferences, and special seminars have been provided, reaching approximately forty physicians and over one hundred registered nurses and allied health personnel. Community lay and medical persons are being contacted to provide input so that the exportability of the program will be insured. Committees will have been formed by May 1981. Due to organizational activities begun as Memorial prepared its CHOP proposal, a 17-bed oncology unit with an all-RN staff, was formed. This unit has accommodated over 500 patients, representing over 5,500 patient days since its opening in April 1980. In addition to the opening of the oncology inpatient unit, an oncology nursing clinic has been established to provide primary care to clinically stable patients. Additional accomplishments include the offering of a CEU-approved Oncology Nursing Education Course on a biannual basis, problem solving clinical rounds for the oncology unit, and institution of an after care and grief follow-up system. By September 1981, a data management plan will be submitted to the National Cancer Institute showing Memorial's ideas regarding gathering, synthesizing, and evaluating all information collected through the CHOP program and to gauge compliance to the patient management plans formulated by a multidisciplinary group of physicians.

Plans: In the coming months, Memorial's CHOP's plans are to develop and define mechanisms for:

- (1) identifying new patients;
- (2) bringing existing and new patients under the patient management guidelines;
- (3) organizing a multidisciplinary consultation team; and
- (4) continuing professional education activities.

In December 1981, the CHOP will submit formal evaluation plans and a program for continuing funding after the federal contract expires.

Project Officer: Donald N. Buell, M.D.

Contract 15551: Community Hospital Oncology Program - Mercy Hospital

From 01/01/81 to 06/30/82

FY 81: \$66,666

Dr. William J. Heim, Mercy Hospital, 746 Jefferson Avenue,
Scranton, Pennsylvania 18501

Objectives: The staff hired for the Northeast Pennsylvania Community Hospital Oncology Program (NEPCHOP) will provide administrative and executive support to facilitate program development. Committees will be established to develop guidelines for the appropriate pretreatment, treatment, follow-up and rehabilitation of the cancer patient. Counseling and supportive care for the cancer patient and family will be addressed as well as standards for nursing care and guidelines. Emphasis will be placed on continued clinical research in cancer care. Education programs will be developed for physicians and other care givers. An evaluation plan will be developed to insure that program components are effective. A plan for future funding to support NEPCHOP will be developed.

Accomplishments: From January 1, 1981 to September 30, 1981. The following staff have been hired: Principal Investigator, Administrative Director, Social Worker, Dietician, Tumor Registrar, Registrar Clerk and Secretary. Each member of the staff will attend conferences outside the institution to upgrade present knowledge related to cancer care. The Principal Investigator and Administrative Director attended the Association of Community Cancer Centers Conference. The Administrative Director will attend the Oncology Nursing Society Congress. The Dietician attended a regional nutrition conference. The Social Worker will attend a conference on cancer and human values. The Tumor Registry Clerk will attend a tumor registrar course and the Registrar will attend a conference to update her present skills and A.R.T. requirements. The Nurse Oncologist will attend the Community Cancer Conference in Indianapolis. A weekly patient care conference emphasizing the multidisciplinary team approach was implemented. The entire NEPCHOP staff attend weekly tumor board conferences. All NEPCHOP committees have been established, meet regularly and expect to develop guidelines for four sites. A terminal care plan will be developed after undertaking a survey to determine the feasibility of an in-patient palliative care unit. A community resource manual is being developed by the Rehabilitation (RCSC) Committee and will be published. An evaluation plan will be submitted and we are interested in a common data set for all CHOP programs. The Administrative Director has been active in delivering three in-service programs to the Nursing staff. The Principal Investigator lectured on NEPCHOP to the HSA Board. He planned the Annual Cancer Symposium on malignant melanoma. He also spoke on two regional television programs, and to medical staffs at Mercy and at affiliated hospitals.

Plans: The NEPCHOP program will emphasize staff and facility development to foster implementation of the guidelines. We will strengthen relationships with comprehensive community cancer centers. A research effort will be supported along with education programs in improving cancer care. A funding plan will be developed as well as an evaluation program.

Project Officer: Donald N. Buell, M.D.

Contract 15552: Community Hospital Oncology Program - The Methodist Hospital

From 01/01/81 to 06/30/82 FY 81: \$144,693
Dr. Sameer Rafia, The Methodist Hospital, 506 Sixth Street,
Brooklyn, New York 11215

Objectives: Brooklyn Community Hospital Oncology Program is a multi-hospital consortium embracing Maimonides Medical Center, Lutheran Medical Center and The Methodist Hospital. Caledonian Hospital is another likely candidate soon-to-be-related to the consortium.

Over 2,000 new cancer patients are registered annually and the catchment area is a large urban center situated in south Brooklyn. Under the auspices of this program, management guidelines both for patient treatment and oncology nursing will be developed and tested in the most common cancer types affecting the community. Monitoring of adherence to guidelines will be carried through the use of a computerized data base which has a united approach in all the consortium hospitals.

Identification of various services for the chronically ill and dying cancer patient in the community and mobilizing this community towards the recognition and rectification of deficiencies in these areas is another major objective.

Accomplishments: Management guidelines for investigation and treatment of the seven most common - in our community - cancer types are developed. Diseases included are those of breast, lung, bladder, prostate, colo-rectum, cervix and malignant lymphomas. The total number of cases which accrue to these sites amount to about 1,200 annually.

A unified form and method of registering all new cancer patients in the consortium hospitals is adopted. Several systems of computerized data management are being investigated and it is expected that an adequate approach will be identified later on this year. Such system is expected to be in place by year end and functioning as soon as implementation phase starts. The systems major features include its ability to monitor treatment guidelines on real-time basis as well as produce multivariate analysis of all cases entered. It will be centrally located but with terminals for input and output in each hospital.

Nursing oncology is being developed in consortium hospitals having increased the total number of nurse oncologists by a factor of 60% (from 5 to 8) as a direct impact of this program. Guidelines for oncology nursing are being developed as well as an extensive education program utilizing all resources available inside and outside the institutions.

Equally active is the professional education arm of the program which has sponsored joint rounds, lectures, symposia, community physician visits to special cancer treatment areas (e.g. radiotherapy) to heighten the awareness of physicians of management guidelines and increase the visibility of the program as a whole. The total number of physicians targeted exceed 1,800 with 1,200 on a regular mailing list. Due to physician cross appointments among different hospitals, other than consortium hospitals, the impact of this program far exceeds its immediate boundaries.

Project Officer: Donald N. Buell, M.D.

Plans: Continue publicizing management guidelines through every avenue giving maximum visibility to pretreatment staging and evaluation in addition to monitoring on real-time basis.

Continue development of data-base concentrating on optimizing its use and applicability.

Identify the various resources of continuing care for the chronically ill and the dying cancer patients in the community.

Develop a plan for optimizing these services and their availability as well as mobilize the community to recognize the need and help bring pressure to bear for rectification of these deficiencies.

Consider including best arms of established group studies in the management guidelines and protocols of respective cancers.

Hold discussions with cooperative groups active in the area about establishing an ongoing relation for clinical investigation.

From 02/16/81 to 08/15/82

FY 81: \$122,022

Dr. Joseph A. Bonta, Riverside Methodist Hospital, 3535 Olentangy River Road
Columbus, Ohio 43124

Objectives: In planning and implementing an organized approach to community cancer care based on a clinical oncology program model three goals are to be achieved:

1. To provide the highest quality of care to the cancer patient seen by well qualified medical and allied health professional staff in modern facilities with the most up-to-date equipment and procedures available.
2. To facilitate the improvement in the quality of cancer care throughout the community through shared educational efforts for physicians, nurses, and allied health professionals.
3. To accomplish quality care by well-trained professionals at the most reasonable cost to the patient and the community.

Riverside is interested in utilizing its cost effective and efficient management system to promote the demonstration model in cancer patient management sought by the NCI for the improvement of cancer patient care throughout the community.

Dr. Joseph A. Bonta, the principal investigator, along with the efforts of over 60 leading members of the Medical Staff, have spent a significant amount of time in the development of the management guidelines.

The management guidelines represent a current acceptable plan of diagnostic and therapeutic management for each of the 16 major cancer sites which include: breast, colon/rectum, prostate, kidney, testis, larynx, endometrium, cervix ovary, vulvar, Hodgkin's disease, urinary/bladder, lung, non-Hodgkin's lymphoma, pancreas and stomach. The Executive Committee of CHOP reviews major policy decisions regarding the operation of the program and makes appropriate recommendations to Medical Council, serves as the designated multidisciplinary committee as required by the American College of Surgeons, acts on the recommendation of the director of the program and is available to the director on a consultative basis with regard to program related matters, communicates to the major hospital departments on the progress of the program and will use its efforts to encourage and enhance the objectives and goals of CHOP to provide better patient care.

The Tumor Board, as designed, provides two purposes; consultative services and professional education. Tumor Board meets weekly for presentation of cancer patients. Tumor Conference is designed for educational purposes only and meets every other month.

The Nursing Care Committee has a broad-based nursing representation with expertise in and responsibility for surgical nursing, chemotherapy, radiation therapy, ostomy care, continuing education, quality assurance and renal, gerontology and oncology clinician nurse specialists.

Project Officer: Donald N. Buell, M.D.

The Rehabilitative and Supportive Care Committee see patients, with their doctors, throughout the hospital to identify problem areas, rehab needs, resources available and discharge planning. Its guidelines will be problem oriented. Each disease entity outlined in the Medical and Nursing Care Guidelines will be covered by the Rehabilitative and Supportive Care Committee.

Riverside Methodist Hospital has been developing its Cancer Data System since early 1980. The requirements of the American College of Surgeons as well as the requirements of a CHOP program have been important factors in the system's initial design. It will be as highly computerized as possible. The system will include casefindings, initial registry, all follow-up (including computer-generated letters), guideline assessment, and patient outcome patterns with on-line data entry, query ability and standard hardcopy output reporting including all logs.

From 04/06/81 to 08/15/82

FY 81: \$111,713

Charles L. Crockett, Jr., M.D., Roanoke Memorial Hospitals, P.O. Box 13367
Roanoke, Virginia 24033

Objectives: Our goal is to develop a community wide, multi-hospital oncology program. In order to attain this goal these objectives have been defined: (1) further enhancing communication regarding cancer care in the consortium hospitals; (2) developing patient management guidelines from medical, nursing and rehabilitative perspectives in order to facilitate increased quality cancer patient care; (3) developing oncology nursing as a specialty in the consortium hospitals; (4) assessing learning needs among health care providers and cancer patients and then; (5) implementing educational programs to meet the needs; (6) establishing a data management plan incorporating collaboration among the consortium hospitals' tumor registries; and (7) developing an evaluation plan to monitor the effects of the CHOP.

Accomplishments: Since the development of the contract proposal, Roanoke Memorial Hospitals and the Veterans' Administration Hospital have established oncology nursing units. In addition, Roanoke Memorial Hospitals have implemented a Hospice Program and the Veterans' Administration Hospital has opened a palliative care unit. In the next six months, we expect to achieve the following: (1) identification of a program director and recruitment of other project staff; (2) establishment of the committee structure necessary to plan and implement the Program; (3) identification of the physicians who are responsible for admitting 75% or more of the cancer patients in the consortium hospitals; (4) preliminary development of several site-specific patient management guidelines; (5) appointment of oncology liaison nurses at the consortium hospitals; (6) initial development of a standardized method of data collection and follow-up through the collaborative efforts of the tumor registries; (7) presentation of a seminar entitled "Caring for the Terminally Ill Patient" to health care providers in southwest Virginia, and (8) development of an evaluation plan, if possible, in cooperation with the other CHOPs and the NCI.

Plans: Since we have only recently begun our program, our plans are directly related to the accomplishments we expect to achieve, as described in the preceding section.

Project Officer: Donald N. Buell, M.D.

From 02/16/81 to 08/15/82

FY 81: \$105,460

Dr. Harry E. Hynes, St. Francis Hospital, 929 N. St. Francis,
Wichita, Kansas 67214

Objectives: The overall objective of the four hospital consortium WCHOP is to assure optimal, multidisciplinary cancer care to the community through the accomplishment of the following: establishment of pretreatment evaluation and staging as well as patient management guidelines by multidisciplinary committees; establishment of cancer nursing guidelines by multispeciality nursing subcommittees; identification of cancer patient and family needs and appropriate assurance of available and utilized rehabilitation and supportive care resources; development of a plan for care of the terminally ill; continual review and update of established guidelines; development and implementation of an effective cancer data management system for evaluation purposes; commitment for continued support and funding for WCHOP beyond the federal funding period.

Accomplishments: By September 30, 1981:

- A. Consortium Committee - recruit and employ Administrative Director, WCHOP.
- B. Physician Site Committees - Complete guidelines for diagnosis and treatment of cancers chosen. Identify site specific information for study through the evaluation system. Submit guidelines to Executive Committee.
- C. Nursing Committee - Identify goals and objectives. Complete all nursing guidelines, submit to physician site committee for review, and submit to Executive Committee.
- D. Evaluation Committee - Interview representatives of Kansas University Data System & American College of Surgeons system as well as other systems. Contract with chosen system. Identify data to be collected and mechanisms of collection. Complete Data Management Plan and submit to Executive Committee.
- E. Rehabilitation & Supportive Care Committee - Complete Terminal Care Plan and Patient Assessment Tool. Identify and Analyze all Community Agency and Supportive Services resources and identify gaps in service.
- F. Executive Committee - Review the following deliverables and refer to consortium hospitals for approval: 1) Terminal Care Plan; 2) Patient Assessment Tool; 3) Data Management Plan; 4) Physician Site Committee Guidelines; 5) Nursing Guidelines.
- G. Approval of Terminal Care Plan & Data Management Plan by consortium hospitals.
- H. Administrative Director - submit first and second quarterly reports to NCI including completed and approved Terminal Care Plan and Data Management Plan.
- I. Advisory Committee - Develop plan for continued funding after NCI funding is over. Disseminate information about WCHOP to community leaders in business, industry, etc.

Plans: At the end of 12 months (February 12, 1982) WCHOP will have completed, gained approval of, and submitted to NCI the following deliverables: Site Specific Guidelines (Medical, Nursing and Rehabilitation); complete evaluation program; extension plan for community resources; terminal care plan; patient assessment tool; a plan for continued funding. During the remaining six months, WCHOP will train data collectors, promote oncology nursing education and public education, and develop cooperative structures to implement the entire program as planned during the first 12 months.

Project Officer: Donald N. Buell, M.D.

Contract 15556: Community Hospital Oncology Program - St. Louis Park Medical
Research Foundation

From 01/01/81 to 06/30/82

FY 81: \$116,086

Dr. J. Michael Ryan, St. Louis Park Medical Center, 5000 West 39th Street,
St. Louis Park, Minnesota 55416

Objectives: The Community Hospital Oncology Program (CHOP) is a community-wide cancer program involving seven West-Metro Minneapolis hospitals. The hospitals have formed a consortium that has as its objective the establishment of a region-wide community and hospital oncology program which will incorporate the entire spectrum of cancer care interventions in order to provide patients and their families with the highest attainable quality of care and quality of life. Changes in patient management will be evaluated and documented.

Accomplishments: Since the program was initiated in January of 1981, twenty-four (24) major committees composed of 190 physicians and 150 allied health professionals have been formed. The committees represent nearly every medical discipline and are drawn from seven hospitals with a combined bed capacity of 3,600 and an annual cancer patient load of 7,000. These committees are addressing ten major objectives relative to cancer care in the community. Expected major accomplishments by the fall of 1981 include the development of multi-disciplinary, state-of-the-art patient management guidelines, mechanisms to assure that specialized treatment protocols and referrals to specialized centers are available; state-of-the-art nursing patient management guidelines; a coordinated hospital-community resource program to assure availability of cancer rehabilitative and appropriate supportive care resources; a modern palliative and terminal care program for pain and symptom management; an education program for physicians, nurses, and other health care personnel; a seven hospital cancer data management system for evaluation of program effectiveness, program accomplishments, assessment of community cancer care practices, and a community endorsed plan for continuation of the program after federal funding ceases.

Plans: The initial planning stage of the program continues to January 1982. During that time all the various guidelines, resource manuals, policies, and other program components will be completed. An implementation plan will be written that encompasses all aspects of the program. Partial implementation of the program has already started but formal implementation begins July 1, 1982.

Project Officer: Dorothy R. Brodie, M.D.

Contract 15557: Community Hospital Oncology Program - St. Luke's Hospital

From 03/16/81 to 08/15/82

FY 81: \$81,695

Dr. Richard J. Torpie, St. Luke's Hospital, 801 Ostrum Street,
Bethlehem, Pennsylvania 18015

Objectives: St. Luke's Hospital of Bethlehem will participate in this program as a single hospital project to field test a model for the development of a multidisciplinary program that will improve the scope and quality of care for cancer patients. The present contract provides an 18-month planning phase to refine methods for maximizing cancer patient care through adaptation and development of clinical, nursing, psycho-social, and rehabilitative patient management guidelines and to plan and implement a program to encourage community cancer care practices in accordance with these criteria. A data management system utilizing existing tumor registry resources will assess changes in community cancer care practices in accordance with these criteria. A data management system utilizing existing tumor registry resources will assess changes in community cancer care practices. It is planned to work with the Center for Social Research at neighboring Lehigh University which will facilitate plans for baseline evaluation as well as methods of impact evaluation within the hospital and the community during the implementation phase.

A two year implementation phase will study and modify the changes in community care and practices.

Accomplishments: This is a new program which is presently in its organizational phase. Initial planning for several educational conferences has been initiated. The present plan is to facilitate the project goals set down for establishing baseline evaluation and for development of specialized multi-disciplinary guidelines. Further strengthening of a model approach of community care will be through the creation of specific nursing care guidelines for oncology patients. This will have a thrust both in the hospital, the nursing school, and within the community. It is also planned to strengthen a really quite excellent tumor registry. It is also hoped that a relationship will be developed through one of the major comprehensive centers or a university cancer center in Philadelphia. This is quite diffuse at this time and the more explicit relationship would probably be advantageous to both the community hospital and the center since definition of this relationship is in itself an important model for future cooperation of other institutions. Plans are also being formulated at this early point to insure matching funding during the implementation phase and methods of self-sustenance of the program following its completion. Methods for documentation and audiovisual display are also being considered in order to provide program viability.

Project Officer: Dorothy R. Brodie, M.D.

Contract 15558: Community Hospital Oncology Program - St. Paul Hospital

From 04/01/81 to 08/15/82

FY 81: \$74,064

Dr. Ronald F. Garvey, St. Paul Hospital Cancer Center, 5909 Harry Hines Boulevard
Dallas, Texas 75235

Objectives:

- A. Establish guidelines for optimal cancer care with particular emphasis on improvements in staging of patients seen at St. Paul.
- B. Improve data management through computerization of the Tumor Registry and improve evaluation of patient care through auditing procedures.
- C. Develop educational programs for patients, nurses, and physicians.
- D. Establish an ongoing relationship with a nearby comprehensive cancer center.
- E. Improve community awareness in support of our cancer activity.

Accomplishments: We hope to have committees formed and active prior to May 1, 1981.

We hope to have data management operative no later than January 1, 1982, and hopefully by October 1, 1981. Ongoing educational programs are already established and include "Caring for the Caregiver," "An Oncology Day for Clergy," which is held on a semi-annual basis, "A Workshop on Breast Self-Examination Instruction for Nurses," and a group sharing project which we term "Learning to Live with Cancer."

Plans: The Executive Committee will formulate plans for completion of the study and ongoing community support of the project.

Project Officer: Donald N. Buell, M.D.

Contract 15559: Community Hospital Oncology Program - St. Peter's Hospital

From 02/16/81 to 08/15/82

FY 81: \$71,982

Dr. Robert W. Sponzo, Albany Regional Cancer Center, P.O. Box 8538,
Albany, New York 12208

Objectives: The purpose of this contract is to develop an implementation plan for a community based oncology program. An appropriate organizational structure will be developed and implemented, consisting of a core project staff, advisory committees, and various program committees. Committees will be selected and implemented to develop programs in cancer education, data management and evaluation, oncology nursing, cancer treatment, and supportive care-rehabilitation. These committees will develop the programs and guidelines essential for the implementation plan to be completed in 12 months.

Accomplishments: The Consortium Committee which oversees the operation of this contract will be formed and will meet in May and September. The Project Staff will implement the program and will see that the component committees accomplish their goals and objectives. The Cancer Education Committee will review and document current educational programs in the region and recommend an improved and expanded educational efforts for public and health professionals. The Data Management and Evaluation Committee will review current data needs and recommend an appropriate computerized data management system for the network. Evaluation criteria will be specified so that the success and impact of the program can be properly determined. The Oncology Nursing Committee will review and document current oncology nursing resources and activities and will develop nursing management guidelines for most malignant sites. The Cancer Treatment Committee will review and document current management techniques being utilized in the region for most malignant sites. This committee will review current treatment resources and will recommend resource improvement and expansion where indicated. This Committee will, also, develop guidelines for physicians for the management of most malignant sites. The Supportive Care-Rehabilitation Committee will review current resources and activities in the region and will recommend improved and expanded programs in these areas. Management guidelines for supportive and rehabilitative care for most malignant sites will also be developed. By August 1981 a data management plan and a feasibility plan for a regional terminal care program will be submitted to the NCI.

Plans: Since this is a planning contract and since our program just began on February 16, 1981, the planning for this program is as previously mentioned.

Project Officer: Donald N. Buell, M.D.

Contract 15560: Community Hospital Oncology Program - St. Vincent Medical Center

From 01/01/81 to 06/30/82

FY 81: \$73,256

Dr. S. Barry Sakulsky, St. Vincent Medical Center, 201 S. Alvarado Suite A.
Los Angeles, California 90057

Objectives: To plan for the implementation of a multidisciplinary community hospital oncology program within a single hospital, involving physicians, nurses, allied health personnel, and the community at large, which will, with the support of a computerized data management system, enable selected inpatients to be managed according to agreed-upon guidelines addressing medical and nursing care and rehabilitation and continuing care, including terminal care when appropriate.

Accomplishments: Between January 1, 1981 and the end of September 1981, the following activities have been or will have been completed: recruitment of program staff; establishment of multidisciplinary committees on overall program direction, oncology nursing medical management, rehabilitation and continuing care, terminal care, and program evaluation; completion of a plan for the data management system/expanded tumor registry which serves as the data base for the program; completion of a terminal care feasibility study identifying needs of SVMC cancer patients with regard to terminal care and estimating potential demand for services; completion of three quarterly progress reports detailing planning activities, committee activities, program successes and difficulties and future plans; preparation of an implementation plan for the Community Hospital Oncology Program at St. Vincent Medical Center, to be submitted to the National Cancer Institute, December 13, 1981.

Plans: This contract supports planning activities only at this point. Additional activities will include assessment of oncology nursing educational needs and resources, implementation of recruitment and education programs for oncology nurses, and implementation of the data management system prior to June 30, 1982.

Project Officer: Donald N. Buell, M.D.

Contract 15561: Community Hospital Oncology Program - South Fulton Hospital

From 02/16/81 to 08/15/82

FY 81: \$33,210

Dr. J. Warner Ray, South Fulton Hospital, 1170 Cleveland Avenue,
East Point, Georgia 30344

Objectives: The planned comprehensive Community Hospital Oncology Program, in addition to further developing the capabilities of existing resources is designed to assure more appropriate and complete pretreatment evaluation and staging of referred cancer patients. Efforts to incorporate multidisciplinary recommendations into patient management decisions will be made. Through developing a working relationship with the University of Alabama, appropriate treatment protocols will be made available for selected patients. In addition, emphasis will be placed on developing a nursing oncology program and on organizing an effective local rehabilitation program. Finally, a component to monitor the program's effectiveness will be conducted.

Accomplishments: A major program accomplishment occurred on November 10, 1980, when South Fulton Hospital opened its 16-bed Oncology Unit. Since November, the unit has recorded 207 admissions. The Radiation Therapy Department has treated 215 new patients from October 1, 1980 through April 30, 1981. The South Fulton Hospital Tumor Registry has abstracted 80% of all 1980 admissions. At present, 503 cases have been abstracted for 1980. The Tumor Registry currently operates with only 4% of its cases lost to follow-up contact. Key grant personnel have attended a total of 9 professional development seminars. These same professionals have organized a Multidisciplinary In-Patient Oncology Conference, which is held weekly on the oncology unit for physicians, nurses and ancillary staff. The conference has met seven times from March 17, 1981 through April 30, 1981. Additionally, a multidisciplinary Tumor Conference is held bi-weekly for physicians, nurses and other appropriate personnel. Other educational efforts include 3/month, 1 hour lectures and discussions dealing with the nurse's role in clinical oncology. The meetings are chaired by the Oncology Nurse Practitioner and are attended by RNs', LPNs' and ancillary nursing staff assigned to the Oncology Unit. Medical, Nursing and Social Work patient management guidelines are currently being designed at the working group level, with input from all appropriate staff members. By August 30, 1981, it is anticipated that a Data Management Plan and a Terminal Care Feasibility Plan will have been developed for this program. Public education and information seminars will also be developed for citizens and residents of the surrounding area.

Plans: To date, plans have involved staff recruitment and committee organization for hospital and community input. Future plans call for the development of patient management guidelines, appropriate professional education activities for nurses, physicians and ancillary personnel, and outreach educational programs for the public. Both a process and impact evaluation of the project is also planned.

Project Officer: Donald N. Buell, M.D.

Contract 15562: Community Hospital Oncology Program - The Toledo Hospital

From 01/01/81 to 06/30/82

FY 81: \$91,200

Dr. Charles D. Cobau, The Toledo Hospital, 2142 North Cove Boulevard,
Toledo, Ohio 43606

Objectives: The goal of the Toledo Community Hospital Oncology Program (TCHOP) - a consortium of three primary care hospitals - is the utilization of a multidisciplinary team approach in the practice of optimal care for cancer medicine. The objectives for realizing this goal include: development of multidisciplinary patient management guidelines; dissemination of and adherence to guidelines by physicians and health-care providers; development and utilization of a data management system capable of assessing the degree of compliance with the guidelines; identification of methods of analyzing data in order to isolate areas of educational efforts to increase voluntary compliance to the guidelines.

Accomplishments: The program has made rapid progress with primary effort being invested in three major areas: recruitment and orientation, operational organization, and programmatic promotion.

The recruitment and orientation of key personnel has been accomplished and includes: the Executive Director and office secretary; physician coordinators for each of the consortium hospitals; chairpersons for the eight standing committees and eleven tumor site specific committees. During the initial planning stage priority attention will be focused on the efforts of the tumor site specific committees and the development of a data management and evaluation plan. Operational organization has included equipping the TCHOP office and evolving procedures for expediting the planning activities generated by the committees. Promotional efforts have been initiated and will be increased as the planning gains momentum.

Plans: Plans for the period from April 15 through September 30, 1981 include: development and approval of a tentative data management plan incorporating the needs of NCI, Clinical Oncology Programs, and local data needs; development of a terminal care feasibility plan which capitalizes on the services provided by the Northwest Ohio Hospice Association; consensus plan for upgrading and coordinating the tumor registries maintained by the consortium hospitals; and, identification of mechanisms for improving referral relationships with geographically appropriate cancer centers.

From October 1, 1981 to July 1, 1982, planning activities will address the following major areas: designation of resources for an oncology nursing program; completion of multidisciplinary guidelines, data management and evaluation plans; identification of strategies for local financial support; and approval by the TCHOP Executive Committee of all tasks enumerated in the NCI contract.

Project Officer: Dorothy R. Brodie, M.D.

From: 01/01/74 to 12/31/82

FY 81: \$111,549

Dr. Morris S. Zedeck, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue,
New York, NY 10021

Objectives: This project has two major objectives: 1) to identify the metabolite of the colon carcinogen methylazoxymethanol (MAM) that is responsible for tumorigenesis, and 2) to identify the exact dehydrogenase enzyme able to metabolize MAM.

A biochemical explanation of the organospecificity of MAM is sought. Identification of the enzyme(s) in colon, liver and kidney that metabolize MAM would allow for studies in chemoprevention and genetics related to colon tumor induction.

Accomplishments: Studies on MAM metabolism indicate that the aldehydic derivative obtained via metabolism of MAM by NAD⁺-dependent dehydrogenase(s), is very unstable and decomposes instantly to liberate carbonium ions. The colon and liver are tissues capable of utilizing MAM as substrate and are especially sensitive to the acute and chronic effects of this agent.

The studies aimed at identifying the active enzymes are ongoing. We have employed various affinity and gel column chromatography procedures to separate out the active enzyme fractions. To date, we have two different fractions, one of which possesses NAD⁺-dependent dehydrogenase activity capable of utilizing MAM as substrate. This fraction is different from the fraction utilizing alcohol as substrate, presumably alcohol dehydrogenase. We will further fractionate this activity using isoelectric focusing combined with histochemical procedures.

Plans: The plan is to continue to identify the active enzymes and to perform in vivo studies with inhibitors of these enzymes to modulate the biological effects of the carcinogen.

Publications:

Zedeck, M.S.: Studies of Factors Relevant to Human Colorectal Carcinogenesis in Animal Models. In Colorectal Cancer: Prevention, Epidemiology, and Screening, S. Winawer, D. Schottenfeld, and P. Sherlock, Eds. New York, Raven Press, 1980: pp. 51-57.

Feinberg, A., and Zedeck, M.S.: Production of a Highly Reactive Alkylating Agent from the Organospecific Carcinogen Methylazoxymethanol by Alcohol Dehydrogenase. Cancer Research, 40:4446-4450, 1980.

Program Director: Vincent J. Cairoli, Ph.D.

Grant CA 15638: Inhibition of Neoplasia of the Large Bowel

From: 01/01/74 to 12/31/82

FY 81: \$123,960

Dr. Lee W. Wattenberg, University of Minnesota, 184 M. Jackson Hall, Minneapolis, Minnesota 55455

Objectives: The major objectives are to produce highly effective inhibitors of chemical carcinogenesis and to identify compounds currently in the environment that have the capacity to inhibit large bowel carcinogens. In the latter category, emphasis will be placed on phenols in the diet.

Accomplishments: A study has been carried out to determine the effect of sodium cyanate in the diet on carcinogenesis of the large intestine under conditions in which sodium cyanate was administered subsequent to all injections of 1,2-dimethylhydrazine (DMH). One hundred female CF-1 mice were given sixteen subcutaneous administrations of 0.6 mg DMH, two times a week for eight weeks. At that time they were randomized by weight into five experimental groups and placed on experimental diets. Three dose levels of sodium cyanate were employed, 1.6, 2.4 and 3.2 mg/gm of diet. Controls were fed diet without any additives. The experiment terminated 42 weeks after the initial dose of carcinogen. The percent of mice with tumors of the large bowel and number of tumors per mouse were as follows: controls, 72% - 3.6 tumors/mouse; sodium cyanate 1.6 mg/gm, 50% - 3.4 tumors/mouse; sodium cyanate 2.4 mg/gm, 42% ($P < 0.05$) - 2.5 tumors/mouse; and sodium cyanate 3.2 mg/gm, 32% ($P < 0.01$) - 2.1 tumors/mouse. The results of this study demonstrate that sodium cyanate exerts an inhibitory effect on DMH-induced neoplasia of the large bowel when administered subsequent to carcinogen exposure. The magnitude of the inhibition is related to the level of sodium cyanate in the diet.

Plans: Studies are currently in progress to test the effectiveness of high molecular weight putative inhibitors of large bowel carcinogens. Other experiments entail determinations of the inhibitory capacities of naturally occurring phenolic compounds on the carcinogenicity of methylazoxymethanol.

Publications:

Wattenberg, L.W.: Inhibition of Carcinogen-induced Neoplasia by Sodium Cyanate, Tert-butyl Isocyanate and Benzyl Isothiocyanate Administered Subsequent to Carcinogen Exposure. Cancer Res., in press, August 1981.

Wattenberg, L.W.: Inhibitors of Chemical Carcinogens. In Cancer: Achievements, Challenges and Prospects for the 1980's, J. Burchenal and H. Oettgen, Eds. New York, Grune & Stratton, 1981: pp. 517-539.

Wattenberg, L.W.: Inhibitors of Chemical Carcinogens. J. Environ. Path. Tox. 3:35-52, 1980.

Program Director: Vincent J. Cairolì, Ph.D.

From 11/01/73 to 11/30/81

FY 81: \$93,112

Dr. Benjamin F. Trump, Professor and Chairman

Department of Pathology, University of Maryland School of Medicine, 10 S. Pine Street, Baltimore, Md. 21201

Objectives: The objectives of this study are to elucidate the mechanisms of carcinogenesis in human prostatic epithelium. Specifically we wish to produce transformation of human prostatic epithelium in vitro as established by tumorigenicity in nude mice, to understand the role of the basal cell in the histogenesis of neoplasia, to explore the role of the cytoskeleton in normal, regenerating, and neoplastic epithelium, to understand the metabolism of chemical carcinogens including polyaromatic hydrocarbons, and to improve the prediction of biologic behavior of neoplastic cells based on modern ultrastructural, cytochemical, and immunocytochemical methods.

Accomplishments: Studies on the cytoskeleton have shown a close correspondence between alterations in certain components and neoplastic transformation in prostatic epithelium. For example, changes in the interaction between microfilaments (actin) and intermediate filaments (keratin), and the plasma membrane may account for loss of plasma membrane specializations (microvilli, cell junctions) leading to alterations in cell shape and social behavior in cultured prostatic adenocarcinoma as compared to normal epithelium. Studies of the metabolism of chemical carcinogens (PAH) have shown induction of enzymes associated with carcinogen activation and binding of presumed electrophilic metabolites to DNA. Xenotransplantation of normal prostate into nude mice has been achieved, and has demonstrated limited phenotypic expression of basal cell types under physiological conditions. A reliable immunohistochemical technique was developed for identification of prolactin and has demonstrated intracellular binding of this peptide hormone, which appeared more marked in poorly-differentiated tumors compared to well-differentiated tumors or BPH.

A number of invited lectures were given relating the changes in prostatic epithelium to the cell biology of disease in this organ, particularly neoplasia.

Plans: Studies will continue on in vitro carcinogenesis, xenotransplantation and effects of microenvironmental influences on phenotypic expression of basal and secretory cells. We will also attempt identification of carcinogenic metabolites and immunohistochemical study of steroid and peptide hormone binding by prostatic epithelium. Data will be used to develop new information on the histogenesis, progression, and prognosis of prostatic cancer.

Publications:

Kahng, M.W., Liu, W., Sanefuji, H., Resau, J. H., Heatfield, B. M., Trump, B. F.: Aryl Hydrocarbon Hydroxylase in Human Prostate. Chem. Biol. Interactions. 1981 (In press).

Program Director: Andrew Chiarodo, Ph.D.

Kahng, M.W., Smith, M.W., Trump, B.F.: Aryl Hydrocarbon Hydroxylase Induction and Binding of Dimethylbenz (a) anthracene in Human Prostate. In Murphy, G.P., Sandberg, A.A., and Karr, J.P., (Eds): The Prostatic Cell: Structure and Function. 1981 (In press).

Trump, B.F., Heatfield, B.M., and Phelps, P.C.: The Role of the Cytoskeleton and Related Components in Normal and Neoplastic Prostatic Epithelium. In Murphy, G.P., Sandberg, A.A., and Karr, J.P. (Eds): The Prostatic Cell: Structure and Function. 1981 (In press).

From: 06/01/74 to 12/31/80

FY 81: -0- (Ann. \$82,633)

Dr. David M. Goldenberg, University of Kentucky, 800 Rose St., Lexington, KY 40536

Objectives: The major objectives of the proposal are to further purify and characterize a GW-39 human colonic carcinoma tumor-associated antigen, colon-specific antigen protein (CSAp); to further improve the assay for CSAp in patient serum/plasma: and, to detect and localize CSAp in various histopathological sections by immunocytochemistry. The model developed as a source for tumor and organ-associated antigens of human colonic tumors has been the human colonic carcinoma xenograft. An in vitro assay of CSAp would be useful in diagnosing and monitoring patients with colorectal cancer. CSAp radioantibodies would have applicability to the radioimmunoassay of colon cancer and might serve as carriers of cytotoxic agents for improved therapy.

Accomplishments: Using the GW-39 human colonic carcinoma grown in unconditioned adult hamsters, two distinct antigenic entities have been identified and isolated. One is a family of colonic organ-specific glycoproteins called colon specific antigens (CSAs) and a distinct organ-specific colonic cancer associated antigen (CSAp). Isolation and purification of CSAp has been partially accomplished. Heteroantisera have been raised and purified by affinity chromatographic techniques. These preparations have been used to develop a sensitive radioimmunoassay for CSAp and have served to monitor the antigen during the isolation and purification steps. Using the assay it has been possible to detect this antigen in the sera of patients with colorectal cancer and to assess its distribution in patients with various disease entities. The results support the view that CSAp is a colorectal cancer-associated antigen which appears to provide useful clinical information regarding the absence or presence of this tumor type in suspected individuals.

Plans: Continued effort will be directed at further purifying CSAp, characterizing it chemically and improving its assay in patients' sera, as well as localizing CSAp in various histopathological sections by immunohistochemistry. A comparison of CSAp isolated from various tumors and tissue sources will be undertaken, including the use of colonic cancer cell cultures. Purified CSAp will be used to produce hybridoma monoclonal antibodies for use in the sensitive assay developed for the detection of CSAp in body fluids. Efforts will continue to expand the antibody array and to define other colon-specific and/or colon carcinoma-specific antigens using the hybridoma technique.

Publications:

Gold, D.V. and Goldenberg, D.M.: Antigens Associated with Human Solid Tumors. In Cancer Markers. Diagnostic and Developmental Significance, S. Sell, Ed., Humana Press, Clifton, New Jersey, 1980, pp. 329-369.

Gaffar, S.A., Pant, K.D., Shochat, D., Bennett, S.J., and Goldenberg, D.M.: Experimental Studies of Tumor Radioimmunoassay Using Antibody Mixtures Against Carcinoembryonic Antigen (CEA) and Colon-specific Antigen-p (CSAp). Int. J. Cancer, 27:101-105, 1981.

Program Director: Vincent J. Cairoli, Ph.D.

From 09/01/73 - 08/31/81

FY 81: \$0 (Ann. \$115,013)

Dr. L.G. Koss, Montefiore Hospital & Medical Center, Bronx, New York 10467

Objectives: Cytologic examination of sediment of voided urine is the principal non invasive diagnostic technique in the initial evaluation of persons suspect of harboring bladder cancer and the principal technique of detection of bladder cancer in high risk exposes to carcinogens. The cytologic evaluation of sediment of voided urine is notoriously difficult. This project has for its purpose objective diagnostic evaluation of cells in the sediment of voided urine by computer-based image analysis. The aims of this research include the formation of a scientific basis necessary for the construction of an automated apparatus for urinary cytodiagnosis by interested industry, and the evaluation of diagnostic and prognostic parameters expressed in the objective analysis of urothelial cells.

Accomplishments: During the years of 1974-1978 the goal of this research was to establish baseline information on the methodology and feasibility of the proposed approach to urinary cytology. Using the TICAS programs developed by Wied et al., it was shown that high resolution images of well preserved mononucleated urothelial cells stained by Papanicolaou method could be discriminated by computer in accordance with visual classification. It was also documented that the diagnosis of bladder cancer could be achieved by constructing cytologic profiles of 12 patients by computer. Subsequently, the file on cells was enlarged to include other types of epithelial cells encountered in the sediment. The misclassification of some cell types, notably degenerated and, to a lesser extent, multinucleated cells was greater than that of mononucleated cells. These analyses were performed on the large dedicated PDP-10 computer at the University of Chicago.

As of 1979 the TICAS analytical programs were implemented on a small laboratory computer at the Montefiore Hospital. During the past 2 years, it was documented that the analysis of cell images on a small computer is feasible with an accuracy closely similar to that obtained on the PDP-10. Patients' profiles, established on 25 patients by computer on mononucleated cells were shown to be of diagnostic significance. A new semi-quantitative technique for preparation of urinary sediment was developed by Bales. It was shown that cell images thus obtained were compatible with images obtained by prior technology. It was also documented that classification of cell images by computer was well within the diagnostic range of experienced human observers. A computer based system of adjustment for staining differences among samples was developed. Because the urinary sediment contains a variety of cell types of varying degrees of diagnostic value, a new concept of hierarchical classification by computer was successfully developed. This approach permits the triage of cell images by computer with an automatic selection of cells of diagnostic significance. The introduction of hierarchical analysis permitted us to study sequential cells in smears and in cytocentrifuge preparations. The patients' profiles obtained by hierarchical analysis of 7

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samples proved to be of diagnostic value and consistent with visual classification. Cytocentrifuge preparations prepared by the Bales' method have been shown to be suitable for high resolution scanning. This approach allows concentration of cells within a circle 6mm in diameter and will serve for the study of sediments with sparse cellularity.

Plans: With minor modifications in the image acquisition system it is planned to validate this research on 100 patients with bladder cancer and 100 controls. The problems of patient-to-patient and sample-to-sample variability will be addressed. A recently started detailed morphometric analysis of the measurable parameters of several thousand cells representing various groups of urothelial cells will provide objective baseline morphologic data and may reveal intragroup differences among cancer cells derived from bladder tumors of various grades and types and data of prognostic significance. Under different auspices, this research may lead to a screening study of workers exposed to bladder carcinogens. The study will provide the scientific background for and documentation to the interested industry that the construction of an automated diagnostic apparatus is feasible and desirable.

Publications: (Periodicals)

Koss, L.G. and Bartels, P.H.: Urinary Cytology. Device Capabilities and Requirements. *Analyt. Quant. Cytol.*, 2: 59-65, 1980

Koss, L.G., Bartels, P.H., A., Sychra, J.J., Schreiber, K., Moussouris, H.S., Wied, G.L.: Computer Identification of Degenerated Urothelial Cells. *Analyt. Quant. Cytol.* 2: 107-111, 1980

Koss, L.G., Bartels, P.H., Sherman, A., Sychra, J.J., Schreiber, K., Moussouris, H.S., Weid, G.L.: Computer Identification of Multinucleated Urothelial Cells. *Analyt. Quant. Cytol.*, 2: 112-116, 1980

Koss, L.G., Sherman, A., Bartels, P.H., Sychra, J.J., and Wied, G.L.: Hierarchic Classification of Multiple Types of Urothelial Cells by Computer. *Analyt. Quant. Cytol.*, 2: 166-174, 1980

Chapters in Book

Bahr, G.F., Bartels, P.H., Wied, G.L., and Koss, L.G.: Automated Cytology, Chap. 31 in Koss, L.G.: *Diagnostic Cytology and its Histopathologic Bases*, 3rd ed., Philadelphia, J.B. Lippincott, 1979, pp. 1123-1164

Bartels, P.H., Koss, L.G., and Wied, G.L.: Automation in Cytology: Computerized high Resolution Scanning of Cervical Smears. Chap. 11 in: Koss, L.G. and Coleman, D., eds.: *Advances in Clinical Cytology*, London, Butterworths, 1981

Periodicals

Herz, F., Schermer, A., and Koss, L.G.: Short Term Culture of Epithelial Cells from the Urine of Adults. *Proc. Soc. Expmntl. Biol. Med.*, 161: 153-157, 1979.

Kahan, A.V., Coleman, D., and Koss, L.G.: Activation of Human Polyoma Virus Infection. Detection by Cytologic Techniques. Am. J. Clin. Path., 74: 326-332, 1980.

Yamase, H.T., Powell, G.T., and Koss, L.G.: A Simplified Method of Preparing Permanent Tissue Sections for the Erythrocyte Adherence Test. Am. J. Clin. Pathol., 75(2): 178-181, 1981

Grant 15945: Studies on Experimental Bladder Tumors

From 12/1/73 - 11/30/82

FY 81: \$171,917

Dr. S.M. Cohen, St Vincent Hospital, Worcester, Massachusetts

Objectives: The objectives of our experiments are (1) to study mechanisms of bladder carcinogenesis using the multistage model of initiation with FANFT followed by promotion with sodium saccharin (SAC), and (2) to examine various morphological and biochemical markers of bladder carcinogenesis and to evaluate their usefulness as markers of the human disease.

Accomplishments: A property of promoting agents is their ability to induce proliferation of the target organ. Sodium saccharin fed as 5% of the diet without prior initiation by FANFT induced bladder epithelial proliferation in male Fischer rats using the sensitive techniques of scanning electron microscopy (SEM) and autoradiography (AR). Quantitative methods were developed for SEM analysis of the bladder mucosa, and using these techniques and AR, a dose response for sodium saccharin-induced mucosal proliferation was demonstrated.

The effect of cell proliferation on initiation and promotion was evaluated using the freeze ulcer method of Shirai to induce reversibly regenerative hyperplasia of the bladder mucosa. FANFT (0.2% of the diet) for 2 weeks followed by SAC for 102 weeks resulted in one bladder cancer. If the bladder was ulcerated and the rat immediately fed FANFT for 2 weeks and then SAC significant incidence of bladder cancer was induced. However, the same results were obtained if the ulcer was followed by 2 weeks of control diet and then SAC or followed immediately by SAC. In addition, diffuse bladder ulceration induced by cyclophosphamide, a mutagen, produced similar results as ulceration by freezing. It would appear that administration of SAC to a rat with a rapidly proliferating bladder mucosa, (in contrast to the normal low mitotic rate) such as following ulceration or *in utero*, is adequate for carcinogenesis without the added presence of a mutagenic initiator. Also, based on previous pellet implantation studies, SAC present for a short time after ulceration followed by a non-specific stimulus of cell proliferation (pellet plus urine) is also sufficient for carcinogenicity.

Long term studies evaluating various properties of 2-stage carcinogenesis in the bladder have been started including length of time between initiation and promotion, necessary time of administration of promotion, and reversing the order of administration of initiator and promoter.

SEM studies of biopsy material from patients with bladder cancer (in collaboration with Dr. George Farro, Mayo Clinic) indicate a variety of abnormal surface features related to cancer with quantitative differences depending on the grade of the tumor. The effects of radiation therapy are also being evaluated in addition to the usefulness of SEM examination of bladder washings and urinary cytologic specimens.

Plans: The long term experiments described above will be completed within the next 18 months. SEM urinary cytology studies will continue with an emphasis

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on quantitation, and experiments examining the kinetics of ulceration, regenerative hyperplasia, and the effects of SAC and FANFT will be performed. In vitro bladder carcinogenesis is being studied in collaboration with Dr. Frank Chlapowski, University of Massachusetts Medical School.

PUBLICATIONS:

Cohen, S.M.: Urinary Bladder Carcinogenesis: Initiation-Promotion. Seminars in Oncology. 6: 157-160, 1979.

Fukushima, S., and Cohen, S.M.: Saccharin-induced Hyperplasia of the Rat Urinary Bladder. Cancer Res., 40: 734-736, 1980.

Cohen, S.M., Tatematsu, M., Shinaohara, Y., Nakanishi, K., and Ito, N.: Neovascularization during Urinary Bladder Carcinogenesis Induced by N-[4-(5-Nitro-2-Furyl)-2-Thiazolyl]Formamide. J. Natl. Cancer Inst. 65: 145-148.

Plotkin, G.M., Gilbert, S.L., Wides, R.J., Wolf, G., Cohen, S.M., and Fukushima, S.: Galactosyl Transferase Activity in Rat Bladder Transitional Cell Carcinoma Lines and in Exfoliated Cells in Urine of Rats during Bladder Carcinogenesis and during Reversible Hyperplasia. Cancer Biochem, Biophys., 4: 251-256, 1980.

Demers, D.M., Fukushima, S., and Cohen, S.M.: Effect of Sodium Saccharin and L-tryptophan on Rat Urine during Bladder Carcinogenesis. Cancer Res. 41: 108-112, 1981.

Fukushima, S., Arai, M., Cohen, S.M., Jacobs, J.B., and Friedell, G.H.: Scanning Electron Microscopy of Cyclophosphamide-induced Hyperplasia of the Rat Urinary Bladder. Lab. Invest., 44: 89-96, 1981.

Murasaki, G., and Cohen, S.M.: Effect of Dose of Sodium Saccharin on the Induction of Rat Urinary Bladder Hyperplasia. Cancer Res., 41: 942-944, 1981.

From: 02/01/74 to 03/31/82

FY 81: \$80,908

Dr. Morris Pollard, The University of Notre Dame, Notre Dame, IN 46556

Objectives: The objectives of this research are to study the pathogenesis of experimentally-induced intestinal cancer, and to develop a reproducible model tumor system which would be of value for assessment of preventive and therapeutic procedures.

Accomplishments: The Lobund strain Sprague-Dawley (S-D) rat is more susceptible to dimethylhydrazine (DMH)-induced intestinal tumors than other rat strains, including the NIH strain S-D rat. When examined after 20 weeks, a dose response to DMH was demonstrable in S-D rats at 30 mg/Kg B.W./week by gavage: 1 dose produced a 70% incidence and 1.4 tumors/rat; 5 doses produced an incidence of 100% and 4.4 tumors/rat. Indomethacin (Indo) was administered in the drinking water (20 mg/L.) to rats after 5 doses of DMH. Indo reduced the incidence of tumors by 40%. In rats with 1 dose of DMH, the incidence of tumor bearing rats was 90% and in Indo-treated rats 20% ($P < 0.0019$). Similar results were demonstrable in rats with methylazoxymethanol (MAM)-induced tumors: one dose of MAM induced tumors in 70% of the rats and this level was reduced to 8% by Indo-treatment ($P < 0.0085$). Intestinal tumors were induced in 75% of rats with 1 dose of methyl(acetoxymethyl)nitrosamine (DMN Oac). In rats administered Indo, the incidence of tumor-bearing rats was reduced to 8%. Thus, a significant reduction of incidence of tumor-bearing rats was demonstrable by treatments with Indo. Similar results were not demonstrable with other prostaglandin-blocking agents; e.g. ibuprofen, aspirin. This autochthonous model system was useful in demonstrating significant beneficial effects of a putative therapeutic agent.

Plans: The role(s) of prostaglandins (PG) in the pathogenesis of intestinal cancer will be further examined to determine if the blocking of PG is the anti-tumor effect of Indo. This will be extended to rats at later stages of tumor development, and to rats following discontinuation of Indo treatments. The effects of Indo will be examined on tumors induced by other carcinogens, N-methyl-N'-nitrosourea (MNU); and in other species (mice) following exposures to DMH and MAM.

The pathogenesis of DMH-induced tumors will be examined in rats receiving high and low fat diets plus Indo in the diets, to determine if PG are actually involved in the tumor-enhancing effect of high fat diets. The role(s) of microflora will be determined in germfree rats in association with defined flora components.

Publications:

Pollard, M., and Luckert, P.H.: Treatment of Chemically-induced Intestinal Cancers with Indomethacin. Proc. Soc. Exp. Biol. and Med., in press, 1981.

Pollard, M.: Metastatic Spread of Experimental Neoplasms. In Metastasis, Clinical and Experimental Aspects, K. Hellmann, P. Helgard, and S. Eccles, Eds. The Hague, Martinus Nijhoff Publishers, 1980; pp. 456.

Program Director: Vincent J. Cairoli, Ph.D.

From 12/01/73 to 11/30/80

FY 81: \$0 (Ann. \$76,999)

Dr. D.F. Paulson, Duke University Medical Center, Durham, North Carolina.

Objectives: The purpose of the present studies is four-fold: (1) confirming the predictive value of the in vitro assay using the athymic nude mouse - human tumor in vivo model, (2) to determine the range of in vitro responses of patients' tumor cells and correlate this information with clinical responses, (3) to assess the degree of heterogeneity in drug sensitivity of primary and metastatic lesions from the same patient, and (4) to evaluate effects of drug combinations utilizing cells from tissue culture and nude mouse tumor lines initiated from patient bladder tumor specimens.

Accomplishments: The predictive value of the assay has been confirmed by a demonstration that the most effective agents identified by the in vitro assay were the same ones which were most effective against the same tumors growing in the nude mouse model. Based on results of assays on patient tumor specimens received to date, each drug appears to exhibit a unique dose-response relationship. Cis-platinum and Adriamycin exhibit significantly steeper dose-response curves than other drugs tested. The range of response of patient tumor specimens to several chemotherapeutic drugs is being defined, but to date, insufficient clinical data has been accumulated in order to set response levels to discriminate between responders and non-responders. Drug response profiles were determined for a primary and a metastatic skin lesion from one patient and also for a nude mouse tumor initiated from that patient's skin lesion. The data indicate heterogeneity among the three sources of cells. Additional data of this type will be needed in order to define the extent of heterogeneity between primary and metastatic lesions. Pairwise combinations of the drugs Adriamycin, bleomycin, cis-platinum, Cytosin, 5-FU, methotrexate and vinblastine are being evaluated for their effects on several different tissue culture and nude mouse bladder tumor lines. Five different nude mouse - human bladder tumor lines, including two new lines established in the past year, provide the majority of the target cells for this study. Several combinations have been highly effective in vitro at very low dose levels.

Plans: This in vitro assay appears to have great potential for providing an information base for the design of individualized chemotherapy programs more effective than standard protocols and for the identification of new drugs and drug combinations of enhanced effectiveness in the treatment of bladder cancer.

Program Director: William E. Straile, Ph.D.

Grant CA 15973: Identification of Colon Cancer Risk by In Vitro Assays

From: 05/01/74 to 02/28/84

FY 81: \$91,211

Dr. Betty S. Danes, M.D., Cornell University Medical College, New York, NY 10021

Objectives: The objectives of this project are 1) to identify in vitro biological properties associated with transformation in monolayer skin cultures which make recognition of increased risk for colonic cancer possible prior to clinical expression; 2) to ascertain the expression of in vitro abnormalities associated with cancer proneness: (a) occurrence of increased in vitro tetraploidy, and (b) alterations in growth kinetics; 3) to determine whether patients with colonic cancer with and without a known genetic basis have qualitative and/or quantitative changes in these in vitro assays; and, 4) to establish human monolayer mucosal cultures from normal appearing mucosa and polyps (with and without germinal mutations for colonic cancer syndromes) for distribution through the American Type Culture Collection (ATCC).

Accomplishments: In vitro studies on dermal cultures from clinically affected and family members at risk demonstrate that the occurrence of increased in vitro tetraploidy was not specific for any one of the cancer-prone genotypes in the heritable colon cancer syndromes studied, but appear to be an in vitro expression, probably one of many so far unrecognized, of cultured skin cells from several of the autosomal dominant heritable colon cancer syndromes (Gardner syndrome, familial colon cancer syndrome in association with discrete polyps, familial polyposis with sebaceous cysts, and heritable colon cancer without polyposis coli) and not for cells with other such germinal mutations (familial polyposis coli with no extra-colonic manifestations and the Turcot syndrome).

A number of phenotypic markers associated with altered growth kinetics of transformation have been observed in monolayer cultures established from full-thickness skin biopsies from patients and some family members at risk for several of the autosomal dominant colon cancer syndrome. These alterations include: ability to grow in low-serum containing medium, increased saturation density and density-independent growth. Such changes in in vitro growth kinetics were not found universally in all affecteds having the same heritable colon cancer syndrome, suggesting heterogeneity within each clinically recognized group. Mucosal monolayer cultures from normal human mucosa have been established for distribution through the ATCC.

Plans: On the basis of the above research, we propose to establish other monolayer cultures from normal appearing human mucosa and polyps for distribution through the ATCC. In vitro research on biological properties associated with transformation in the colonic cancer syndromes will continue to further delineate culture and clinical phenotypes aimed at identifying members at risk for colonic cancer prior to clinical expression. We will also evaluate the occurrence of increased in vitro tetraploidy in a normal population to test our hypothesis that this cell marker may be detecting a cancer prone gene(s).

Publications: Danes, B.S., Bulow, B., and Svendsen, L.B.: Hereditary Colon Cancer Syndromes: An In Vitro Study. Clin. Genet., 18:128-136, 1980.

Program Director: Vincent J. Cairoli, Ph.D.

Grant 15978: Patterns of Care Study

From 02/20/74 to 05/31/84

FY 81: 0 (Ann. \$1,194,710)

Dr. Simon Kramer, Department of Radiation Therapy, Thomas Jefferson University,
1025 Walnut Street, Philadelphia, Pennsylvania 19107

Objectives: The Patterns of Care Study in radiation therapy is a nationwide evaluation of the practice of radiation therapy involving radiation oncologists in all types of practice. The study's objective is to improve the quality and the accessibility of radiation therapy care. The rationale is that differences do exist across all types of practice; these differences can be studied and documented; these differences are important in the outcome of treatment; these differences can be modified; the effect and impact of these modifications can be measured and documented. This study has examined the profile of radiation therapy as it is being practiced including initial consultation and diagnosis of the patient, localization and treatment fields, and administration of daily therapy, and follow-up efforts after treatment is completed.

Accomplishments: Substantial data analysis has been completed in all six PCS Outcome disease sites. Scientific papers have been prepared in cervix and seminoma of the testis. Drafts of papers in Hodgkin's disease, larynx, anterior tongue, and prostate are in progress. Each of these papers reports national outcome data for major complications and recurrences in the given disease site. A fourth facility master list is in preparation and a paper describing the other three facility surveys has been submitted for publication. Each facility master list describes the profile of radiation therapy in the United States in terms of equipment, patient load, and personnel. Comprehensive process criteria have been developed for Hodgkin's disease and a resurvey at facilities has yielded data showing a relationship between adequacy of mantle field delivery and outcome. Comprehensive criteria will be developed for larynx and cervix as well. The study will report its findings to the practicing radiation oncologist and will also be initiating educational programs to bring the most important findings directly to the discipline.

Plans: In 1981, a national process/outcome study will be initiated. This study will collect national data in three disease sites for both process and outcome. In addition, specific investigation of detailed clinical questions will be undertaken. These efforts will be ultimately directed towards development of a quality assessment program which will be offered to the practicing radiation therapist through the auspices of the American College of Radiology accreditation program, but based entirely on the experience and mechanisms developed by PCS.

Publications:

MacLean, C. J: Variation in workup and treatment procedures among types of radiation therapy facilities: The Patterns of Care process survey for three head and neck sites. Cancer (IN PRESS)

MacLean, C.J.: Discriminant analysis of radiation therapy procedures. The Patterns of Care process survey for carcinoma of the larynx. Cancer (IN PRESS)

Program Director: Donald N. Buell, M.D.

Hanks, G.E., Herring, D.F., Kramer, S.: Patterns of Care Outcome Studies:
Results of the national practice in seminoma of the testis. Int J Radiat Oncol
Bio Phy (IN PRESS)

Grant 16263: Effects of Carcinogens on Macromolecular Events

From 07/01/78 to 06/30/81

FY 81: 0 (Ann. \$43,983)

Dr. Owen Black, Jr., Section of Gastroenterology, Department of Medicine,
Medical College of Georgia, Augusta, Georgia 30902

Objectives: The objective of this project is to observe metabolic changes occurring in pancreatic tissue following exposure to a variety of carcinogens. Efforts were made to determine changes that occur in transcriptional and translational processes in pancreatic tissue. We hoped to determine from these studies what nuclear processes were altered following carcinogen administration, whether the carcinogens had a common mode of action, and how these alterations ultimately related to the tumorigenic processes.

Accomplishments: In the previous reporting period we had observed that 7, 12-dimethylbenzanthracene (DMBA) treatment resulted in significant changes in DNA content, RNA content and rates of protein synthesis. Because of the reported coordination of RNA synthesis with ornithine decarboxylase (ODC) enzyme activity, we examined the effects of DMBA on ODC activity. Such studies suggested that ODC was closely correlated with RNA synthesis and perhaps occurred as a result of such synthetic activity rather than the cause of the response. Exposure of tissues to benzo(a) pyrene (BP) following the same protocol as with DMBA, demonstrated a qualitatively similar response although the extent of response and the time of response differed between the studies. Changes in RNA synthesis lagged ODC enzyme activity suggesting that ODC might have influenced rates of RNA synthesis. The major difference between the studies was in effect on protein content and rates of synthesis. With DMBA treatment there was no change in protein content and decreased rates of synthesis. Following BP there were changes in protein content and a biphasic change in rates of synthesis. The extent to which these changes in nuclear events influence the ultimate tumorigenic process remain to be seen.

Plans: This is the final reporting period for this project. We have proposed a change in direction in the subsequent years to examine the relationship between the effects of these carcinogens on ODC and the resultant ODC activities in pancreatic neoplasms.

Publications:

Black, O., Brazier, N. and Gaffney, S. P.: Changes in deoxyribonucleic acid and ribonucleic acid content protein synthesis, and ornithine decarboxylase activity in rat pancreas following 7, 12-dimethylbenz(A)anthracene treatment, J. of Environmental Path. Tox., In press.

Program Director: William E. Straile, Ph.D.

Grant 16365: Etiology of Urogenital Tumors

From 03/01/74 to 02/28/82

FY 81: \$91,583

Dr. Fred Rapp, Department of Microbiology, The Pennsylvania State University
College of Medicine, Hershey, Pennsylvania 17033

Objectives: The overall objective of this project is to determine the etiology of urogenital tumors. In the current year, we are studying biological and immunological properties of cloned lines of human cytomegalovirus (HCMV)-transformed human embryo lung cells. It has been observed that the percentage of CMV-transformed cells expressing virus-specific antigens gradually decrease with increasing passage levels. Concomitantly with this decrease in viral antigen expression, the tumorigenicity of these cells increases. The purpose of this study is to examine the mechanism by which CMV-transformed cells lose their viral antigens and become more oncogenic during prolonged in vitro cultivation.

If these observations are relevant to human tumors, it may not be possible to detect CMV antigens (or nucleic acids) in prostatic tumors. Selection may result either in negative cells or in cells expressing minimal virus-specific information.

Accomplishments: We have observed that the loss of antigenicity and the increase of tumorigenicity of uncloned CMV-transformed HEL cells during prolonged in vitro cultivation is most probably due to spontaneous selection of tumorigenic cell variants already present in early passages of the uncloned transformed cell culture. Apparently, tumorigenic cells represent only a minority of the young total cell population. Results from experiments have shown that the majority of nontumorigenic cells express CMV-related antigens. Some cell lines tested, however, were negative. A tumorigenic cloned cell subline did not express CMV-related antigens.

Plans: The specific plans for this grant on the etiology of urogenital tumors include:

- a. To grow prostatic and other urogenital epithelioid tumor cell cultures for (a) establishment of cell lines and, (b) test for herpesvirus-makers (in situ hybridization.)
- b. Normal epithelioid cells of prostatic origin (from BPH tissues) will be transformed with HSV and HCMV in vitro.
- c. Original tumor tissues will be tested for human herpesvirus genetic information using the in situ hybridization technique.
- d. Seroepidemiologic study of prostatic cancer patients, including black population groups and the prospective method of investigation.

Program Director: Andrew Chiarodo, Ph.D.

Publications:

Geder, L., Ladda, R., Kreider, J., Sanford, E. and Rapp, F. Properties of Human Epithelioid Cells Transformed In Vitro by a Herpesvirus IBRV (HMC) Isolated from Cytomegalovirus-transformed Human Cells. J. Natl. Cancer Inst., 63: 1313-1321, 1979.

Geder, L. and Rapp, F. Herpesviruses and Prostate Carcinogenesis. Archives and Andrology 4: 71-78, 1980.

Geder, L., Lee, K., Dawson, M., Hyman, R., Maliniak, R. and Rapp, F. Properties of Mouse Embryo Fibroblasts Transformed In Vitro by Infectious Bovine Rhinotracheitis Virus. J. Natl. Cancer Inst., 65: 441-450, 1980.

Grant CA 16375: The Role of Bile Acids in Etiology of Large Bowel Cancer

From: 06/01/74 to 04/30/81

FY 81: -0- (Ann. \$60,331)

Dr. William H. Elliott, St. Louis University School of Medicine, 1402 South Grand Blvd., St. Louis, MO 63104

Objectives: The objective of this research is the definition of a relationship of bile acids or their derivatives to the etiology of large bowel cancer. Specifically, we propose to ascertain the effects of diet on the nature and amounts of bile acids in the hepatobiliary circulation and in the lumen of the colon. Gas liquid chromatography, thin layer chromatography, radioassay, and mass spectrometry will be employed to separate, identify and measure the quantities of conjugated bile acids in the enterohepatic circulation.

Accomplishments: Rats having cannulas inserted into the common duct and either the duodenum or jejunum were used to study the secretion of bile salts from the liver. Hepatic secretion of bile salts responded to the nature of the diet if all bile collected was returned except for a small sample retained for analysis. Where bile was returned at rates slower than the rate of hepatic secretion, the secretion of bile salts from the liver was correspondingly reduced and diet had a diminished effect. From the rates of secretion and return of bile, it was possible to calculate the "minimum rate of hepatic biosynthesis" (MRHB) of bile salts. The MRHB was inversely related to the rate at which bile salts were returned to the duodenum and appeared to depend, in part, on the diet consumed.

If bile was returned to the jejunum instead of the duodenum, the MRHB was significantly lowered. Thus, due to the shorter time of mixing with food or bacterial contents of the alimentary tract, the bile salts infused into the jejunum are more efficiently resorbed into the enterohepatic circulation and the liver is not required to synthesize bile salts at as rapid a rate. Studies in which [^{14}C] taurocholate was administered via the duodenum or via the jejunum demonstrated that absorption of this bile salt is nearly instantaneous from the latter site.

Plans: Project terminated April 30, 1981.

Publications:

Elliott, W.H.: Identification of Sterols and Bile Acids by Computerized Gas Chromatography - Mass Spectrometry. *Lipids*, 15:764-769, 1980.

Shaw, R., Riventa, M., and Elliott, W.H.: Bile Acids LXIII. Relationship Between the Mobility on Reversed-phase High-performance Liquid Chromatography and the Structure of Bile Acids. *J. Chromatog.*, 202:347-361, 1980.

Program Director: Vincent J. Cairoli, Ph.D.

From; 06/01/74 to 07/31/81 FY 81: -0- (Ann. \$106,717)
Dr. Bandaru S. Reddy, American Health Foundation, Naylor Dana Insititute for
Disease Prevention, 1 Dana Road, Vahalla, NY 10595

Objectives: The overall objective is to explore systematically the key intestinal metabolites by which a high-risk person for large bowel cancer can be identified and which will provide information on the specific substances responsible for large bowel cancer in man. The aims are to 1) study the levels of fecal bile acids and cholesterol metabolites and the fecal bacterial enzymes of symptomatic, asymptomatic and healthy members of cancer families who are at high- and low-risk for the development of large bowel cancer; 2) study the mutagens in the feces of the above study populations; and, 3) identify key biochemical indicators which distinguish high- and low-risk populations for the development of large bowel cancer.

Accomplishments: In attempts to improve the surveillance of subjects at high-risk for cancer of the large bowel, namely members of hereditary colon cancer prone (CCP) families, we have determined fecal cholesterol degradation as a marker that will identify these subjects before the development of advanced disease. In the CCP symptomatic group, all subjects previously affected with colon cancer had cholesterol degradation below the normal range, with mean fecal cholesterol 16.4 mg/g dry feces, and mean percent degradation of 33%. In controls, the mean level of fecal cholesterol was 3.2 mg/g dry feces and mean percent cholesterol degradation was 85%. Fecal mutagens of three populations with distinct risk for the development of colon cancer were studied: healthy male subjects from Kuopio, Finland (low-risk), vegetarian Seventh-Day Adventists (SDA), and non-Seventh-Day Adventists (non-SDA) from New York. In the case of SDA, none of the samples tested showed mutagenic activity in any of the tester systems, whereas 13% of Kuopio samples exhibited activity in only TA98 without S9 activation, 11% of samples mutagenic in TA100 without S9 and 9% of samples in TA100 with S9 activation. In general, the fecal extracts of the non-SDA consuming a high-fat, high-meat, low-fiber diet showed a higher mutagenic activity than did volunteers from Kuopio consuming a high-fat, high-fiber diet.

Plans: We plan to isolate and identify the mutagens in the feces of healthy subjects who exhibit high fecal mutagenic activity.

Publications:

Reddy, B.S., Sharma, C., Darby, L., Laakso, K., and Wynder, E.L.: Metabolic Epidemiology of Large Bowel Cancer: Fecal Mutagens in High- and Low-risk Population for Colon Cancer. Mutation Res., 72:511-522, 1980.

Lipkin, M., Reddy, B.S., Weisburger, J., and Schecter, L.: Non-degradation of Fecal Cholesterol in Subjects at High Risk for Cancer of the Large Intestine. J. Clin. Invest., 67:304-307, 1981.

Program Director: Vincent J. Cairoli, Ph.D.

From 07/01/74 - 06/30/82 FY 81: \$289,000 est.
Dr. David Schottenfeld, Memorial Sloan-Kettering Cancer Center
1275 York Avenue, New York, New York 10021

Objective: The program is designed to improve prevention, detection, diagnosis, treatment, and rehabilitation of cancer in community hospitals and agencies through: (1) development of regional baseline data regarding cancer incidence, mortality, and community health resources; (2) audit of medical records to evaluate the variation in quality of site-specific cancer care; (3) education programs directed toward the public and health professionals; (4) special project development. Development and maintenance of a network of community hospitals and community health care agencies has been the major organizational mechanism used to meet these objectives. A Steering Committee from Memorial Sloan-Kettering Cancer Center and the Regional Advisory Board have advised the Office of Cancer Control regarding program priorities as well as specific activities.

Accomplishments: (1) Development of The New York Metropolitan Breast Cancer Group, administrative assistance given to the Memorial Adjunct Staff Oncology Group, the Head and Neck Society of New York City, and the New York Metropolitan Breast Cancer Group. (2) Continuing input into the activities of the Cancer Communications Office of Memorial Sloan-Kettering Cancer Center with special emphasis directed toward the development and evaluation of educational activities for students, union members, minority groups and the general public. (3) Assistance provided to community hospitals in upgrading the quality of hospital records by providing a standardized means of recording and evaluating patient care both in the community and at the comprehensive center. (4) Development, implementation and evaluation of a medical record audit of 554 colon-rectal cancer patients admitted to ten community hospitals and Memorial Sloan-Kettering Cancer Center. (5) Development of a computerized cancer resources data base for New York and New Jersey to be used in conjunction with cancer incidence and mortality data in planning network hospital expansion and program development. (6) Development of survey instruments to evaluate quality of social work care with the cancer patient, the impact of family physician practice on cancer patients, (particularly in minority communities) and health beliefs and attitudes of Black New Yorkers in relation to cancer. (7) On-going collaboration with MSKCC staff and network hospital staff to perform professional education needs assessments, plan and coordinate education programs, and develop evaluation tools to assess the impact of programs on participants from the region. The education activities include: making regular MSKCC courses available, responding to requests for speakers, developing workshops and regional conferences, and co-sponsoring lecture series. (8) Administrative and financial assistance to community hospitals for development, implementation, and evaluation of local cancer control projects related to screening, detection, hospice care, rehabilitation, patient and public education. (9) Distribution of pamphlets, records and tapes for patients, health care workers, and the general public.

Plans: Specific future plans for the MSKCC Office of Cancer Control include:
(1) Update resource data base particularly in New Jersey and combine with cancer incidence and mortality data base; (1) Implement social work, family

Program Director: Carlos E. Caban, Ph.D.

physician, and Black New Yorker survey instruments; (3) Carry out breast cancer audit in network hospitals; (4) Implement feasibility study regarding development of breast cancer audit; (5) Expand network hospital relationships into areas targeted by baseline data analysis, with special emphasis on inner city areas; (6) Expand evaluation activities to other discipline-specific education areas; (7) Special project development with a particular focus on cancer prevention.

From 06/01/74 to 06/30/82

FY 81: \$221,084 est.

Dr. Gail Hongladarom, Fred Hutchinson Comprehensive Cancer Center
1124 Columbia Street, Seattle, Washington 98104

Objectives: The Fred Hutchinson Cancer Research Center is the focus of cancer control activities in the State of Washington, and works with cancer programs in other states in the Pacific Northwest to stimulate cancer control studies, programs, and activities. Several objectives can be specified; (1) Implement and evaluate ongoing projects and activities; (2) Identify and develop relationships with a regional network of organizations; (3) Compile, analyze, and disseminate existing data resources; (4) Identify and implement needed programs; (5) Develop a comprehensive cancer control plan for the Northwest/Alaska region.

Accomplishments: The four professional staff direct one-third time to planning, implementing and evaluating public and professional education programs. Annual conferences and symposia have been conducted for physicians, nurses, social workers, and the clergy. Management Guidelines were completed for cancer rehabilitation and for use of the Hickman catheter. An Oncology Self Learning Facility provides audiovisual materials to health professionals and the public. A bi-annual Biology of Cancer eight-week program and a series of lectures on Cancer Pain Management have been offered. The Tumor Board Consultant Program sponsored medical oncologists, pathologists, surgeons and other specialists to attend the tumor board in cancer conferences in distant communities. A six-week physician seminar series was sponsored for physicians to stimulate dialogue and interaction between center-based scientists and community practitioners. A continuing education calendar of all major cancer related professional educational programs has been included in the Quarterly Report published by the Center. A Breast and Testicular Self-Examination program and a Biology of Cancer program have been offered to high school students, and a cancer control program for older adults has been initiated. The Cancer Control Program has co-sponsored numerous educational and service activities, events, and programs with organizations throughout the region. It has coordinated the Northwest Pacific Hospice Committee and has operated a Nurse-to-Nurse consultation program. The Cancer Data Specialist and Health Planner have been collecting and analyzing baseline cancer data (e.g., incidence, mortality, distribution of programs and services, etc.) in Washington and throughout the Northwest region. An analysis of stage at diagnosis for the major sites by county has been initiated in Washington State.

Plans: To develop a comprehensive regional cancer control plan based on the systematic analysis of regional needs. To plan and implement cancer prevention programs for older adults and for employees. To improve and continue to offer ongoing needed programs. To develop cancer control program evaluation methods.

Publications:

Hongladarom, T. and Hongladarom, G.: The Problem of Testicular Cancer: How Health Professionals Can Help. Accepted for publication in Military Medicine.

Program Director: Carlos E. Caban, Ph.D.

Hongladarom, G., McCorkle, R., and Woods, N.: The Women's Health Book
Englewood, Cliffs, New Jersey, Prentice-Hall, Inc. In Press.

Hongladarom, Gail and Mary McDonell: Using Statistical Data in Cancer Control
Program Planning in Progress in Cancer Control. Alan R. Liss, Inc.,
Publisher. New York. 1981

Hongladarom, Gail: Answers to Questions About Cancer. The P.E.O Record.
February 1981.

Hongladarom, G.: Outreach Programs: Past, Present, and Future. Nursing
Administration Quarterly. Vol. 4(4), pp. 85-88. Summer 1980.

Porter, S.: Breast and Testicular Self Exam. Seattle, Wa., Fred Hutchinson
Cancer Research Center, 1980, 16 pp.

Grant CA 16405: Developmental Cancer Control Program - Wisconsin

From 06/01/74 to 12/31/82

FY 81: \$428,653

Dr. Robert O. Johnson, Wisconsin Clinical Cancer Center, University
of Wisconsin, 1900 University Avenue, Madison, Wisconsin 53705

Objectives: Rationale and significance of this project: In order to decrease the morbidity and mortality of human cancer in Wisconsin, the objectives of this program have been reviewed and endorsed by the Wisconsin Council for Cancer Control, a representative multi-specialty consumer advisory body to the Center. Of primary significance are ongoing programs in public information and education, prevention, diagnosis, treatment, and evaluation of the worth of these objectives and their impact on planning and legislation. Professional education programs translate the current research and validated experimental conclusions to treatment and rehabilitation information for Wisconsin's health care professionals.

Accomplishments: Wisconsin Clinical Cancer Center Cancer Control Activity, fiscal year 1981: (1) We have completed a cancer rehabilitation needs assessment program for WCCC. (2) We have begun the cancer prevention clinic in University Hospital and have isolated a number of pedigree families for study. (3) We have identified network programs for the Wisconsin Oncology Group. (4) We have completed an interdisciplinary evaluation of our Cancer Information Service utilizing biometry support from the Cancer Control Program. (5) We have prepared an in-depth evaluation summary for continuing education programs. (6) We have initiated developmental projects to assess the statistical impact of cancer in Wisconsin, developed a research model to assess the rationale for cigarette consumption in primary school children, established two cancer control studies in pain control for cancer, in addition to supplying support services for our cancer pain management, and have initiated two independent epidemiological studies of non-Hodgkin's lymphoma and chlorinated water.

Plans: To establish independent research programs and cost-benefit analyses of cancer patient management and prepare publishable papers on all phases of cancer control, similar to those listed under publications on this report.

Publications:

Development of Service and Research Program in Cancer Etiology and Prevention in a University Hospital, Richard R. Love, M.D.
WCCC Cancer Rehabilitation and Continuing Care Needs Assessment Study Report, Habeck, Blandford, Sacks and Mallec.
Wisconsin Cancer Information Service 1980 Non-Professional Caller Survey Study Report, Roston and Blandford.
Wisconsin Clinical Cancer Center Patient Education Needs Assessment, Nowobieski.
The Critical Role of Needs Assessment in Post-Graduate Medical Education, Richard R. Love, M.D.
The Efficacy of Screening for Carcinoma of the Prostate by Digital Examination, Richard R. Love, M.D.
The Value of Screening, Richard R. Love, M.D. and Anthony E. Camilli, M.D.
A Course in Cancer Prevention for Practicing Physicians, Richard R. Love, M.D.

Program Director: Carlos E. Caban, Ph.D.

Grant CA 16408: Sidney Farber Cancer Control Developmental Grant

From 06/01/74 to 06/30/82 FY 81: \$466,155 est.

Dr. W. Bradford Patterson, Sidney Farber Cancer Institute, 44 Binney Street,
Boston, Massachusetts 02115

Objectives: The overall objective of the Sidney Farber Cancer Institute's Cancer Control Program is to improve the quality of cancer care in the community. This goal is implemented through professional education for physicians, nurses, social workers and pharmacists; public information; affiliations with community hospitals; promoting regionalization of cancer control through subcontracts to other Boston specialized cancer centers; pilot studies and research; and planning and evaluation.

Accomplishments:

SIDNEY FARBER CANCER INSTITUTE CANCER CONTROL PROGRAM:

Outreach: includes nine community hospitals and networks in Massachusetts and Maine; semi-annual clinical trials conferences for physicians; accrued 103 patients to SFCI protocols.

Social Work Oncology Group (SWOG): developed 10 regional groups which are becoming self sufficient; professional education included 2 week-long courses on "Social Work with Cancer Patients"; 2 day-long symposia; and 40 regional programs. SWOG News is distributed monthly to 2,500 health professionals.

Communications Office: provide toll-free telephone Cancer Information Service; public education efforts targeted at employees at the worksite and minority populations; weekly newspaper columns throughout New England; funded separately through NCI.

Research: "Improvement in Terminal Care Through Phase Congruence", studying the hypothesis that optimal management of the terminal patient requires congruence in treatment objectives among patient, physician and family; developed by the Division of Cancer Control and funded by NCI in September 1980.

Regional Coordination: Regional Cancer Control Committee (RCCC), 13 member consortium, promotes interinstitutional programs, provides a peer review for cancer control proposals, and reviews legislation and public policy issues; distributed Smoking curriculum Resource Guide to 2,300 public and private Massachusetts schools accrued 102 patients in 1980 to joint protocols in sarcoma, mesothelioma, and melanoma.

Massachusetts Cancer Nursing Network (MCNN): jointly developed with American Cancer Society (Massachusetts Division) to facilitate regional planning and implementation of cancer nursing activities across Massachusetts.

Cooperative Cancer Planning Project: Cancer Control Component for 1980 State Health Plan adopted (first cancer control plan in U.S.); drafted standards and measures in radiation therapy.

Program Director: Carlos E. Caban, Ph.D.

MASSACHUSETTS GENERAL HOSPITAL: CANCER CONTROL OFFICE:

Education: conducted 7 smoking cessation clinics for hospital employees; held third annual Health Education Program on smoking in conjunction with ACS's Great American Smokeout; breast cancer symposium for hospital employees; completion of 2 public education films by MGH Television Department, sponsored by Massachusetts Division of ACS.

Outreach: extended formally to 5 community hospitals; programs vary according to needs of individual hospitals.

Research and Regional Coordination: Development of multi-institutional pilot project to determine if elderly cancer patients can be predetermined to be "at risk" for institutionalization. Development and implementation of televised smoking cessation research project with MDPH. Planning of RCCC/MHA program "The Hospice Concept and Its Integration into the General Hospital - A Program for All Caregivers", scheduled for May 1981.

TUFTS NEW-ENGLAND MEDICAL CENTER CANCER CENTER:

Cancer Center programs have continued to develop with the recognition that the tertiary center has an obligation to the affiliated hospitals and the community, including a wide variety of clinical and education programs.

REGIONAL ONCOLOGY PROGRAM - HUBERT H. HUMPHREY CANCER RESEARCH CENTER
BOSTON UNIVERSITY AND UNIVERSITY HOSPITAL:

Clinical Trial Networks: establishment of mechanisms to enable community physicians to place patients on protocol studies; educational programs for physicians, nurses, social workers and paramedical staff; development of a computer-based record system for cancer care for use in community hospitals.

Outreach: extended formally to 8 community hospitals and the Pilgrim Foundation for Medical Care of Southeastern Massachusetts (HMO); includes educational activities, tumor boards, consultations, and direct clinical consultation.

Education: designed and expanded Regional Oncology Nurses' Clinical and Education Project (RONCEP), a comprehensive, multidisciplinary program to provide continuing academic and clinical education in cancer to community-based staff nurses; educational offerings in oncology included 5 workshop series and 14-week college oncology course at Bridgewater State and Stonehill Colleges on "Cancer: A Public Health Issue".

Plans: The SFCI Regional Cancer Control Program will continue its focus on improving community-based cancer care by: 1) assisting defined group of physicians and community hospitals to participate in clinical trials and adhere to baseline standards of management (e.g. through professional education); 2) conducting research into factors which influence such participation and adherence; 3) promoting regional coordination; and 4) selectively disseminating and evaluating public education. In order to promote adherence to agree-upon standards of management, we intent to target our research and control efforts to the physician community.

PUBLICATIONS

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Heller, K.S. Changing Guidelines for Cancer Detection Exams. Physician East 3:8-9, 1981.

Heller, Karen S. Deciding the Safety of Diagnostic X-rays, Physician East, November, 1980

Lived Long? Live Well! 18 minute slide-tape and user's manual on colo-rectal cancer, 1980 (available through Division of Cancer Control, Sidney Farber Cancer Institute).

W. Bradford Patterson, M.D., Karen H. Antman, M.D. Advances in the Management of Soft-Tissue Sarcomas in Adults, Current Concepts In Oncology, Vol. 2, No. 3, Fall, 1980.

Pediatric Oncology/Hematology Newsletter. Winter, Summer, Fall, 1980.

Regional Cancer Control Committee. Hospice: A Massachusetts Perspective, 1980 (available through Division of Cancer Control, Sidney Farber Cancer Control, Sidney Farber Cancer Institute).

Regional Cancer Control Committee. Primary Breast Cancer: Recommendations for Diagnosis and Treatment, 1980 (available through Division of Cancer Control, Sidney Farber Cancer Institute).

Regional Cancer Control Committee. Smoking Prevention: Bright Ideas for Smoking Education Programs in Schools, An Annotated Resource Guide, 1980 (available through Division of Cancer Control, Sidney Farber Cancer Institute).

From 06/01/75 to 06/30/82

FY 81: \$249,000 est.

Dr. Curtis Mettlin, Roswell Park Memorial Institute, 666 Elm Street
Buffalo, New York 14263

Objectives: The overall objective of the Cancer Control Program at Roswell Park Memorial Institute (RPMI) is to provide efficient and effective dissemination of information, technologies and skills to improve the care of the cancer patients in Western New York and nearby areas of Pennsylvania and Ohio and to enhance the prevention and early detection of cancer in the population served. Specifically, we seek to: 1) continue collaborative cancer control programs with regional hospitals, medical societies, universities and other organizations in the fields of cancer treatment, prevention, detection and rehabilitation, 2) improve the processes of patient referral to insure that cancer patients receive prompt, appropriate treatment for their disease, 3) demonstrate efficient and effective approaches to the screening of high-risk populations suited to implementation in the community and train health professionals in cancer detection, 4) provide community practitioners and allied health professionals with up-to-date guidelines on cancer prevention, diagnosis, treatment and continuing care, 5) collect and analyze data pertinent to needs assessment and program planning, identification of target audiences, patterns of cancer care and regional trends in cancer incidence, 6) evaluate program impact by studies of behavior change in program participants, monitoring of program effort, and impact of patterns of physician referral and other appropriate evaluation standards.

Accomplishments: Oncology Seminars were conducted in collaboration with the Erie and Niagara County Units of the American Cancer Society, the State University of New York at Buffalo, area hospitals and medical specialty societies. Roswell Park Memorial Institute staff visited twenty-two area hospitals in New York and Pennsylvania on fifty-two occasions to meet with local physicians for a total of 1,131 outreach contacts. Activities ranged from regular participation in tumor conferences, lectures, and seminars to collaboration in radiotherapy. Eightyone Cancer Teaching Days were held in different locations in New York and Pennsylvania. These programs provide the public with factual information on cancer cause and prevention. Institute staff initiated a program of monthly multidisciplinary conferences held in different Buffalo area institutions on a rotating basis. In collaboration with the New York State Tumor Registrars Association the staff of the Western New York Tumor Registry organized the annual two-day seminar for hospital tumor registrars. The Nursing Department and Cancer Control Department collaborate in the planning and presentation of several seminars yearly for nurses through: a) Outreach Programs in community hospitals, and b) Cancer Teaching Days in cooperation with the American Cancer Society, and other nursing groups as well as programs offered at Roswell Park Memorial Institute. In association with the New York State Division of the American Cancer Society, Cancer Control and other Roswell Park staff have prepared a program on instruction on proper breast self-examination practice for nurses. Program guidelines have been developed. This program has been adopted for statewide implementation by the B.S.E. subcommittee of the New York State Division of the American Cancer Society. Community outreach at Roswell Park consisting of face-to-face programs on cancer prevention and early detection in schools, civic groups, and senior citizens organizations was conducted.

Program Director: Carlos E. Caban, Ph.D.

This program particularly serves ethnic and economically disadvantaged and other medically underserved persons, in the Buffalo area. A genetic counseling program provides clinical assistance in advising patients and their families of possible genetic risks for their specific cancers. Counseling involves the joint activity of a clinician and human geneticist.

Plans: Program plans include: 1) further development of utilization of Roswell Park Memorial Institute Comprehensive Cancer Center resources and services by physicians, other health professionals, community organizations, and lay persons in the Western New York region, 2) conduct educational programs for professionals and lay persons in the target audiences' own communities as well as at Roswell Park Memorial Institute, 3) develop and evaluate impact of community outreach program aimed at high risk, medically underserved minority populations, 4) assess effectiveness of Breast Self-Examination program designed to upgrade BSE skills and practice by lay and professional women, 5) utilize registry data to assess changes in cancer patterns which may reflect on cancer control impact in regions served, and 6) undertake developmental projects aimed at further improving the patterns of cancer patient care, further understanding the prevention and detection health behaviors of the populations served and promoting public utilization of cancer prevention, detection, and information resources.

Publications:

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From 06/30/74 to 11/30/83

FY 81: \$326,555

Robert C. Hickey, M.D., University of Texas System Cancer Center,
Houston, Texas 77030

Objectives: The objectives of this project are to investigate and determine risk factors in individuals and the community to add new knowledge to the cancer control base; to provide education for nurses and primary care physicians in the early detection and diagnosis for the control of cancer before health is affected; and to provide education and communication to professionals and lay public for the primary control of cancer.

Accomplishments: A Division of Cancer Prevention has been established and organized around three operational components: Preventive Epidemiology, Health Maintenance, and Health Education. Based on existing data resources and the "Impact of Cancer in Texas" study large ethnic differences in cancers of the breast (females) and colon (males and females) among Whites, Blacks and Spanish-surnames individuals have been found. A field program relating these differences to dietary and nutritional factors is being established. An Interagency Center for Cancer Prevention and Control has been established. This Interagency agreement is a joint partnership between the UTSCC, the Texas Department of Health and the Texas Division, ACS. The committee meets monthly and has jointly sponsored a revised second edition of the "Impact of Cancer in Texas", a risk evaluation of occupational workers for individual counseling, evaluation of cancer of the cervix in Texas to facilitate more appropriate control measures, and a study of the economics of cancer prevention in Texas. In the Health Maintenance area, over 250 nurses have been trained in cancer screening and education. Two 20 minute films have been produced to teach nurses how to conduct breast self-examinations and how to take a risk factor history. An Employee Screening and Education Clinic has been piloted and was found to be highly successful. A permanent Preventive Medicine Clinic is being established. A prevention lecture series for professional education is established and five speakers have presented lectures. Evaluation is completed for the nurses' screening and breast self-examination programs and for the Employee Screening Clinic.

Plans: Plans are underway for a smoking cessation program for employees, for a permanent Preventive Medicine Clinic for screening and education of high risk groups, for development of an etiologic patient history, for a study of cancer prevention economics in Texas, and for an expanded health education program.

Publications:

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Program Director: Carlos E. Caban, Ph.D.

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The Cancer Detection and Screening Program. The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute.

Prevention and You ... The Unbeatable Two. A Benefit for Employees of the University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute.

From 05/01/74 to 04/30/82

FY 81: \$53,258

Dr. Cecil H. Robinson, Department of Pharmacology and Experimental Therapeutics,
Johns Hopkins University School of Medicine, 725 N. Wolfe Street, Baltimore,
Maryland 21205

Objectives: The objectives of this project are the continued biological study of 5,10-secosteroids which we have previously shown to be in vitro inhibitors of prostatic 5 α -reductase. Studies of prostatic 5 α -reductase inhibitors in vivo in rats, and of effects on other steroidogenic tissues such as adrenal and testis should pave the way for in vivo studies in Dunning tumor-bearing rats. Other new potential irreversible inhibitors of 5 α -reductase will be synthesized and tested.

Accomplishments: Animal studies are being carried out, using 5,10-secosteroids such as 5,10-seco-19-norpregna-4,5-diene-3,10,20-dione. These studies are intended to examine their inhibitory effects on rat prostatic 5 α -reductase in vivo, and to study their effects in other tissues such as adrenal and testis. These studies were intended to lead to studies in the Dunning R3327-H tumor. New allenic steroids which may be potential irreversible inhibitors of 5 α -reductase are being synthesized and will be tested in vitro with rat prostatic 5 α -reductase.

Plans: The compounds described above will be evaluated for prostatic 5 α -reductase activity in vivo in rats, as well as for tissue specificity and for beneficial activity in the Dunning R-3327-H tumor in rats.

Program Director: Andrew Chiarodo, Ph.D.

From 06/01/76 to 06/30/82

FY 81: \$331,000 est.

Dr. Robert McKenna, University of Southern California,
1721 Griffin Avenue, Los Angeles, California 90031

Objectives: The Regional Activities Program (RAP) is the official cancer control arm of the Los Angeles County-University of Southern California Comprehensive Cancer Center. It is the goal of the Regional Activities Program to develop and demonstrate techniques of transferring improved methods of cancer prevention, detection, diagnosis, treatment, continuing care, and rehabilitation from the research environment to the health professionals, organizations, institutions, agencies, and general public in the community. This goal is accomplished directly through the development of education, communication and service programs by the RAP that are provided and/or developed with the community and indirectly by supporting, encouraging and facilitating cancer control activities of the other organizations, groups, and individuals in the community. Through RAP the cancer center is providing leadership in the development of programs involving active participation of the health practitioners, organizations, institutions and agencies in the community. The cancer center is serving as a focal point for community efforts to assure the widespread use of the best available methods for early detection and treatment of cancer, collection of data useful in the prevention and cure of cancer, and dissemination of information, both at the lay and professional levels.

Accomplishments: (1) Through the efforts of RAP, 101 hospitals have obtained the approval of the Commission on Cancer of the American College of Surgeons in the region. (2) The Cancer Management Network of the RAP has grown to include 26 hospitals throughout Southern California. Member hospitals of the Cancer Management Network have: surveyed all educational activities within member hospitals, evaluated the quality of Tumor Board presentations in several of the hospitals, and conducted a retrospective audit of breast carcinoma treatment in several member hospitals. (3) RAP published a cancer resource inventory of member hospital resources, developed the mechanism to carry out research treatment protocols in participating Network hospitals, developed a study to analyze the prognostic value of estrogen and progesterone receptors, and developed a Nursing Education committee. (4) Evaluation plans have been developed to monitor and measure the performance of many of the RAP implemented programs and are presently being conducted. (5) 95 registered nurses have completed a continuing education curriculum in oncology to prepare them for work in oncology units, clinical cancer facilities and inpatient education programs in cancer. (6) 30 nurses have been educated to become enterostomal therapists. (7) 29 tumor registrars have completed training during 1980-81 and are now working in area cancer data collection activities at community hospitals. (8) Three hundred seventy-six cancer education programs were conducted in 180 community hospitals throughout the region. Total attendance for those programs was 8,000 physicians, 680 nurses, 153 tumor registrars and 400 other health-care professionals. (9) Five major cancer education symposia were held, reaching 250 physicians, 74 registered nurses, 98 clergy and 25 allied-health professionals.

Program Director: Carlos E. Caban, Ph.D.

Plans: We plan to implement extensive evaluation activities in all programs and to develop independent support for as many regional programs as our evaluation indicates. We plan to work with a number of epidemiologists to initiate studies of various cancer control activities particularly in the area of screening. We will plan with other investigators to develop other cancer control modalities for study and evaluation and demonstration.

Publications:

McKenna, R.J: The Role of the Hospital Cancer Program in Cancer Control. in Burchenal, J. H. and Oettgen, H. F. (Ed.): Cancer Achievements, Challenges, and Prospects for the 1980's. N.Y., Grune & Stratton, 1981, Vol. 1, pp. 743-753.

From 05/01/74 to 04/30/81

FY 81: (Ann. \$107,055)

Dr. Noel R. Rose, Department of Immunology and Microbiology, Wayne State University, School of Medicine, 540 E. Canfield Avenue, Detroit, Michigan 48202

Objectives: Tumor immunology is based on the concept that tumor cells express antigens that are not found in normal cells and that the host can recognize them as immunologically foreign. The discovery of such tumor antigens in human neoplasms is expected to serve as a basis for immunotherapy and immunodiagnosis of malignant disease.

The aim of project is to determine whether the specific cytotoxic T-lymphocytes of prostatic cancer patients recognize antigens that are unique to malignant prostatic epithelial cells. Another objective of this research is to study the surface antigens of human prostatic cancer cells by use of the murine and human hybridoma systems.

Accomplishments: During the past two years technical aspects of lymphocyte fractionation and cultivation and of a cytotoxic T-lymphocyte assay based on lll in release have been thoroughly investigated in this laboratory. Furthermore, the contribution of NK cell activity to the cytotoxic activity of prostatic cancer patients has been elucidated. However, we found that the development of clinically useful cytotoxic T-lymphocyte assay requires rather large amounts of autochthonous tumor cell cultures and T-lymphocytes. Extensive efforts were made to grow human prostatic cancer cells in culture or as a transplant in nude mice. Primary cultures can yield up to 10^7 cell and tumors survive a few months as a transplant in the nude mice. However, antigenic studies of tumors require a continuous supply of tumor cells and cytotoxic lymphocytes with consistent immunological specificity and biological characteristics. With the recognition of these restrictions in the development of a CTL assay, now we are investigating prostatic antigens and tumor antigens by the use of hybridoma-derived antibodies and cloned CTLs recognizing prostatic cancer cells. For the production and characterization of murine and human hybridoma antibodies, we are using a portion of the tumor mass as the immunogen while the rest of the tumor are stored frozen. Immunohistological characterization of monoclonal antibodies requires only thin sections of tumor and other tissues. The technical procedures of generating hybridomas and cytotoxic T lymphocyte clones have been established in our laboratory.

Plans: We will define the most prominent surface antigens of prostatic cancer by means of hybridomas secreting antibodies to normal prostatic cells and tumor cells. We will study in detail the basic conditions for the establishment of cytotoxic T-lymphocyte clones using DU-145 and PC-3 as a model system and then to extend the study to the autochthonous prostatic cancers.

Program Director: Andrew Chiarodo, Ph.D.

PUBLICATIONS:

Frost, P., Rose, N.R., Choe, B.K., and Pontes, E.J.: Immunology of Prostatic Carcinoma, In E. Spring-Mills and E.S.E. Hafez (Eds.), Accessory Sex Glands of the Male Reproductive Tract, Chapter 17. Elsevier/North Holland, New York. 311-326, 1980.

Choe, B.K., Pontes, E.J., and Rose, N.R.: Methods for the Detection of Human Prostatic Acid Phosphatase, in Manual of Clinical Immunology (Rose, N.R. and Friedman, H. Eds.). American Society for Microbiologist, Washington, D.C., pp. 951-962. 1980.

Choe, B.K., Rose, N.R. and Pontes, E.J.: Chapter 12 Radioimmunoassay for Human Prostatic Acid Phosphatase in E.S.E. Hafez and E. Spring-Mills (Eds.) Prostatic Carcinoma Biology and Diagnosis, Martinus Nijhoff BV Publishers, Hague, Netherlands. pp. 131-140, 1980.

Choe, B.K., Pontes, E.J., Dong, M.K. and Rose, N.R. Double-antibody Immunoenzyme Assay for Human Prostatic Acid Phosphatase. Clin. Chem. 26: 1854-1859, 1980.

Choe, B.K., Pontes, E.J., Lillehoj, H.S., and Rose, N.R. Immunohistological Approaches to Human Prostatic Epithelial Cells. The Prostate. 1: 383-398, 1980.

Choe, B.K., Dong, M.K., Walz, D., and Rose, N.R.: Antibody Restores Catalytic Activity of a Small Molecular Weight Fragment of Human Prostatic Acid Phosphatase, Molecular Immunol. (In press), 1981.

Choe, B.K. and Rose, N.R.: Chapter 17, Immunological Assays of Human Prostatic Acid Phosphatase, In Busch, H. and Yeoman, L.C. Eds. Methods in Cancer Research, Academic Press, New York. (In press), 1981.

Rose, N.R., Choe, B.K. and Pontes, E.J.: Chapter 14 Prostatic Acid Phosphatase, in Ablin, R. Ed. Science and Practice of Surgery, Marcel Dekker, Inc. New York, (In press), 1981.

Grant 16736: Prostatic Fluid in Diagnosis of Prostatic Cancer

From 06/01/76 to 08/31/82

FY 81: \$0 (Ann. \$48,351)

Dr. John T. Grayhack, Department of Urology, Northwestern University, 633 Clark Street, Evanston, Illinois 60201

Objectives: The principal objective of this project is to identify changes in the prostatic fluid composition that are discriminatory characteristics of patients with carcinoma of the prostate. Recognition of these changes has a significant potential to assist in achieving the following goals: (1) Provide an important additional technique for identification of patients with carcinoma of the prostate or those at high risk of developing prostatic cancer, (2) Provide information that may lead to the development of other procedures that will assist in identifying this group of patients, and (3) Provide a possible means of identifying variations in biological activity of prostatic carcinoma.

Accomplishments: Our major effort has been the continuous evaluation of complement C3, transferrin and LDH-5/LDH-1 ratio in prostatic fluid collected from patients in our Urology Clinics. Due to the limited volume of fluid collected each time, the preference has been the analysis of complement C3 and transferrin. LDH determinations are carried whenever the extra fluid is available. Since the last report (July, 1980), the following additional patients have been evaluated:

Patient Groups	Number of patients (1/1/80-1/15/81)			Number of patients (cumulative)		
	C3	TF	LDH	C3	TF	LDH
Cancer	15	17	16	62	60	99
BPH	26	28	--	85	88	140
BPH + WBC	6	7	--	33	32	52
Prostatitis	43	55	20	107	105	306
Normal	24	23	7	58	56	229

The determination of C3 and transferrin in the prostatic fluid has continued following our initial observation of elevated levels in men with carcinoma as compared to those with no evidence of cancer, including men less than 45 years of age, patients with BPH and prostatitis. The mean of all determinations in patients with cancer exceeds the highest of the means of non-cancer patients by almost 3 times for both C3 and transferrin concentrations. The difference persists when a mean of the lowest value of each patient is used. For the C3 determination, if a 95% of the lower values in the non-cancer groups (10 mg/100 ml) is accepted as the value dividing normal from cancer, only 16% of accumulated cancer patients will have a value in the normal range. Likewise, 95% of the values for transferrin of all non-cancer patients are below 30 mg/100 ml and only 26% of cancer patients are in this normal range.

LDH-5/KDH-1 ratio in the prostatic fluid is also consistent with our original observations. Approximately 75% of the patients with malignancy and 15% of patients with BPH without inflammation had a ratio of LDH-5/LDH-1 of 2 or more.

Program Director: Andrew Chiarodo, Ph.D.

The majority of patients with prostatitis also have a ratio of 2 or more. All men under 45 years of age without evidence of prostatic inflammation have ratios less than 2.

Plans: Currently in progress is the preparation of all laboratory and clinical data for computer storage and process. This effort will facilitate our ability for data retrieval and data analysis. We plan to continue searching for parameters in the prostatic fluid that can improve our ability to identify men with prostatic cancer or having a high risk of developing one. Analysis of prostatic acid phosphatase by RIA has been renewed to confirm our earlier impression of a low PAP activity in the fluid from cancer patients by the enzymatic method. Identification of acid and basic iso-proteins for ferritin will be attempted, since the acidic type of ferritin is known to be associated with malignancy and the basic type is with the normal tissue. The detection of prostatic fluid for the presence of a specific antigen associated with prostatic cancer is also planned in collaboration with Dr. T. M. Chu of the Roswell Park Memorial Hospital.

Publications:

Journal Articles:

Grayhack, J.T., Lee, C., Kolbusz, W. and Oliver, L.: Detection of Carcinoma of the Prostate Utilizing Biochemical Observations. *Cancer* 45:1896-1901, 1980.

Grayhack, J.T., Lee, C., Oliver, L., Schaeffer, A.J. and Wendel, E.F.: Biochemical Profiles of Prostatic Fluid from Normal and Diseased Prostate Glands. *The Prostate* 1:227-237, 1980.

Grayhack, J.T. and Bockrath, J.M.: Diagnosis of Carcinoma of Prostate. *Suppl. Urology* 17:54-60, 1981.

Schaeffer, A.J., Wendel, E.F., Dunn, J.K. and Grayhack, J.T.: Prevalence and Significance of Prostatic Inflammation. *J. Urol.* 125:215-219, 1981.

Book Chapters:

Lee, C., Jesik, C., Uke, E., Falkowski, W. and Grayhack, J.T.: Prostatic Neoplasia: Clinical and Experimental. In: Nagasawa, H. and Abe, K. (Eds.): Hormone Related Tumors Japanese Scientific Societies Press, Tokyo (In Press).

From: 01/01/75 to 06/30/81

FY 81: -0- (Ann. \$75,530)

Dr. Selwyn A. Broitman, Boston University School of Medicine, 80 East Concord St., Boston, MA 02118.

Objectives: The major objective is to identify nutritional factors which contribute to the high incidence of colon cancer. The studies are focused on the role of dietary and endogenous cholesterol and its metabolites in the gut lumen on large bowel tumorigenesis in an experimental model. The effects of dietary cholesterol on initiation and promotion of tumorigenesis will be ascertained and the effects of dietary-induced lowering of serum cholesterol levels will be determined in this model. The relationship of dietary polyunsaturated and saturated fat to the disbursement of cholesterol systemically and/or enterally will be evaluated. It is anticipated that the data will provide a better understanding of the relationship of nutrition, the microflora, and colon cancer, and perhaps suggest guidelines aimed at the prevention of colon cancer through nutritional intervention programs.

Accomplishments: Studies conducted in male Sprague Dawley rats fed a variety of diets consisting of either 20% saturated fat (coconut oil) or 20% unsaturated fat (safflower oil) with or without cholesterol and/or cholic acid have lead to several findings: 1) a polyunsaturated fat diet without cholesterol and cholic acid is not significantly different than a saturated fat diet without cholesterol and cholic acid on dimethylhydrazine (DMH)-induced large bowel tumor incidence and number; 2) the addition of cholesterol and cholic acid to a high fat diet increases the incidence and number of DMH-induced large bowel tumors, whereas the addition of cholesterol alone and cholesterol with cholic acid increases the number of tumors above those fed only a saturated fat diet. However, cholic acid when added to a high fat diet without cholesterol did not increase the number of gastrointestinal tract tumors. The addition of either cholesterol or cholic acid or both to the various diets increased the fecal excretion of both neutral and acid sterols.

Neomycin feeding augmented large bowel tumorigenesis in rats fed a safflower oil diet, but inhibited tumorigenesis in rats fed a safflower oil, cholesterol and cholic acid diet. No relationship was seen between the concentration of either neutral or acid sterols in feces and the number of large bowel tumors. However, a shift in the composition of fecal sterols to secondary bile acids was observed in association with increasing numbers of large bowel tumors.

Plans: Efforts will continue to ascertain the relationship of dietary cholesterol and cholic acid in combination with saturated and unsaturated fat diets on the incidence, number, size, and type of large bowel tumors induced by DMH. Fecal excretion of neutral and acid sterols will be assessed further. The comutagenic effects of various fecal neutral and acid sterols will be evaluated in the Ames assay. The effects of dietary alterations on T-lymphocyte and natural killer cell activity and on the immunogenicity of transplanted bowel tumors will be assessed. Similar studies will be conducted using other carcinogens.

Publications: Broitman, S.A.: Cholesterol Disbursement and Colon Cancer. Cancer Research, in press, 1981.

Program Director: Vincent J. Cairoli, Ph.D.

From: 06/01/74 to 05/31/81

FY 81: -0- (Ann. \$55,758)

Dr. Benjamin Drewinko, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, 6723 Bertner Avenue, Houston, TX 77030

Objectives: The aim of this project is to evaluate the activity of antitumor agents on cultured human carcinoma cells. Drug-induced cytotoxic and cytokinetic effects are studied on different colonic cell lines with varying degrees of differentiation. A major part of the project involves the further characterization of several established colon carcinoma cell lines and the development of in vitro models that reflect the behavior of quiescent cells in vivo. In addition, we intend to develop an in vivo system for xenografting colorectal carcinoma cells in nude athymic mice.

Accomplishments: Our studies have confirmed the hypothesis that colorectal carcinoma cells can be segregated into three separate biological groups according to their morphological differentiation, karyotype, deoxyribonucleic acid (DNA) content, rate of carcinoembryonic production, and cytokinetic properties. The cytotoxicity of twenty antitumor drugs has been evaluated on exponentially-growing and stationary-phase cells. The data demonstrate that virtually every drug is more effective on proliferating cells. Fluorinated pyrimidines, delivered for one hour, had modest lethal activity on five colorectal carcinoma cell lines. Cell killing increased if treatment was prolonged for extended periods of time. The activity of nitrosourea derivatives (BCNU, Methyl-CCNU, CCNU, cis-acid and PCNU) was defined. Cytotoxic and cytokinetic activity of pyrazolo-imidazoline and N-(phosphonacetyl)-L-aspartate have been evaluated. A powerful synergistic effect of ara-C and cis-platin was demonstrated, providing the rationale for a clinical trial with this combination. The cytotoxic and cytokinetic activity of vinca alkaloids (vincristine, vinblastine and vindesine) was established. Methyl-GAG was demonstrated to be an ineffective agent when delivered for brief periods of time. The activity of AMSA and anthracenedione was evaluated. Two separate xenograft systems were established in our laboratory; one utilizing the athymic nude mouse and the other the Rowett athymic nude rat. Both systems allow the propagation of human colorectal carcinoma cell lines. Preliminary in vivo studies with 5-Fluorouracil were conducted using the nude mouse system.

Plans: Cytotoxic and cytokinetic activities of various new antitumor agents (prospidine, CC-1065, Nogalamycin, methyl-GAG, 1,4-cylcoheradiene-1,4-dicarbamic acid, 2, 5-bis (1-azridinyl) 3,6-dioxo, diethylesper (AZQ) alone or in combination with known antitumor agents will be evaluated both in vitro on established cell lines and in vivo using the xenograft system. In addition, the in vivo studies will include an evaluation of nutritional manipulations of growth kinetic properties to observe possible enhancement of the antitumor effect.

Publications:

Bergerat, J-P., Drewinko, B., Corry, P. and Ho, D.H.: The Synergistic Lethal Effect of Cis-Dichlorodiammineplatinum and Arabinosylcytosine. Cancer Research, 41:25-30, 1981.

Program Director: Vincent J. Cairoli, Ph.D.

From 05/15/71 - 04/30/83

FY 81: \$95,447

Dr. C.C. Irving, University of Tennessee Center for the Health Sciences
and VA Medical Center, Memphis, Tennessee

Objectives: The overall objective of this project is to determine the biochemical mechanisms involved in the induction of bladder cancer in rats with N-butyl-N-(4-hydroxybutyl) nitrosamine (BHBN) and its major urinary metabolite, N-butyl-N-(3-carboxypropyl)nitrosamine (BCPN). This project is part of our overall program on the study of organ and species specificity in chemical carcinogenesis. The hypothesis being tested in this project is that a stable precursor of an activated metabolite derived from BCPN is formed in the liver and is excreted in the urine, where it undergoes hydrolysis (either intravesically or intracellularly after absorption) with liberation of an activated metabolite. If this cannot be proven, then BCPN itself is metabolically activated directly by rat bladder epithelial cells.

Accomplishments: We have previously reported that disulfiram (DSF) significantly inhibited the induction of bladder cancer in male Wistar rats exposed to BHBN (Irving et al, Cancer Res., 39:3040, 1979). If BCPN is a proximate carcinogenic metabolite of BHBN, and the main effect of DSF is to inhibit conversion of BHBN to BCPN, then DSF should have little effect on the induction of bladder cancer with BCPN. To test this, adult male Wistar rats were divided into 6 groups of 30 rats each: (1) control diet; (2) control diet containing 0.5% DSF; (3) control diet plus 1.5mM BHBN in the drinking water; (4) control diet containing 0.5% DSF plus 1.5mM BHBN in the drinking water; (5) control diet plus 1.5 mM BCPN in the drinking water; and (6) control diet containing 0.5% DSF plus 1.5mM BCPN in the drinking water. The rats were kept on these regimens for 12 weeks and were then transferred to and maintained on control diet until sacrificed at 30 weeks. There were no significant differences in the intake of nitrosamines within the groups. After fixation *in situ* and removal, all bladders were examined grossly under a dissecting microscope and then microscopically after sectioning at 3-4 mm and staining with H & E. Bladder neoplasms were classified according to stage and grade. The incidences of bladder cancer at 30 weeks were: group 1, 0/30; group 2, 0/30; group 3, 24/30 (80%), mostly transitional cell carcinoma, stage A, grade II; group 4, 2/30 (7%), each stage 0, grade I; group 5, 30/30 (100%), mostly stage A, grade III; and group 6 3/30 (10%), each stage 0, grade I. Thus, it is clear that DSF significantly inhibited the induction of bladder cancer in rats exposed to BCPN (group 6 vs group 5, chi-square = 45.5, P-valued < 0.001). We also confirmed our previous results on the effect of DSF on BHBN carcinogenesis (group 4 vs group 3, chi-square = 29.9, P-value < 0.001). We have also shown that DSF does not appear to significantly affect the conversion of BHBN to BCPN *in vivo*. For these studies, 0.5% DSF was given in the diet to male Wistar rats. After 2 weeks of DSF administration 14-C labeled BHBN (3.3 mCi/mmmole) was given intraperitoneally (25 mg/kg) and the urine and expired carbon dioxide were collected for 8 hrs. The amount of radioactivity excreted was determined. There was no difference in the excretion of total radioactivity in urine

Program Director: William E. Straile, Ph.D.

between control rats (84.4% in 8 hrs.) and those pretreated with DSF for 2 weeks (85.3% in 8 hrs.). Although the total radioactivity in expired carbon dioxide was low in both groups, there was a significant reduction (44%, $P=0.02$) in the rats treated with DSF (0.58% in 8 hrs.) compared to control rats (0.97% in 8 hrs.). The amount of BCPN excreted in urine was not affected by pretreatment with DSF: control rats, 61% of dose as BCPN/8 hrs. and DSF-treated rats, 55% of dose as BCPN/8 hrs. These data, taken together with the carcinogenicity data, clearly demonstrate that DSF is influencing one or more steps in the further metabolic activation of BCPN.

Grant 16880: Bladder Cancer: Immunology, Immunotherapy and Virology

From 07/01/74 to 09/31/81

FY 81: 0 (Ann. \$275,654)

J.L. Fahey, UCLA School of Medicine, Los Angeles, California

Objectives: The objectives of this project are to define significant antigenic changes occurring in human transitional cell carcinoma so as to gain insight into the mechanisms of bladder carcinogenesis, as well as to develop improved diagnostic (and prognostic) and therapeutic modalities.

Accomplishments: We have utilized the technique of murine hybridoma antibody production to select antibodies which react with human TCC tumor-associated antigens. This has generated a panel of cell lines secreting unlimited amounts of antibodies recognizing several cell surface antigens. Spleen cells from mice immunized against a human TCC cell line, 647V, were fused to a murine myeloma cell line with polyethylene glycol and the cells selected in vitro for fusion products between the two cell types. Supernatants from wells containing viable cells were tested for reactivity to the immunizing 647V cells by an antibody-staph protein A binding assay. Of the 200 wells tested, initially 12 percent were positive. Subsequently 13 hybridoma antibodies were also tested against 647V, another human TCC cell line, T24, and a human lung squamous cell carcinoma cell line, P3. Two were positive against all three targets, one was positive against 647V and P3, three were positive against 647V and T24, and seven were positive against 647V only. Thus, at least four separate antigens were detected. Data concerning the reactivity of these hybridoma antibodies against normal tissue, TCC tumors, and other TCC cells will be presented.

Plans: Production and screening of hybridoma antibodies would be facilitated by having TCC cell lines for which autologous tissue culture lines of B-lymphoblastoid and fibroblasts were available. To aid in the establishment of TCC in tissue culture we have developed a new culture medium which specifically promotes epithelial cell growth while suppressing fibroblast growth. In initial studies, 2/3 bladder washing specimens cultured in this medium demonstrated growth of adherent cells with epitheloid morphology which may represent establishment of new cell lines.

Publications:

Bloom, E.T., and Brown, D.E.: Detection of antigenic differences and similarities between human transitional cell carcinoma cell lines using rabbit antisera. Urol. Res. 8:5-13, 1980.

Brosman, S.: Immune response in bladder cancer. In: Bladder Tumors and Other Topics in Urological Cancer. (Eds. M. Pavone-Macaluso, P.H. Smith, and F. Edsmyr), Plenum Publishing Corp., pp. 125-147, 1980.

Dorey, F. and Zigelboim, J. Immunologic variability in a health population. Clin. Immunol. and Immunopath. 16:406-415, 1980.

Program Director: William E. Straile, Ph.D.

Lichtenstein, A., Zighelboim, J., Dorey, F., Brosman, S., and Fahey, J.L.: Comparison of immune derangements in patients with different malignancies. Cancer 45-2090-2095, 1980.

Brosman, S.: Immunotherapy in bladder cancer. In: Bladder Tumors and Other Topics in Urological Cancer. (Eds. Pavone-Macaluso, P.H. Smith, and F. Edsmyr) Plenum Publishing Corp., pp. 165-170, 1980.

Blight, Jr., E.M., Biggers, R.D., Soderdahl, W.D., Brosman, S.A., Lamiell, J.M. and Raleigh, E.N.: Bilateral renal cysts and tumor occurring in a patient with a family history of renal tumors. J. of Urol. 124:695, 1980.

From 06/01/75 to 11/30/81

FY 81: 0 (Ann. \$51,681)

E. Brill, Ph.D., University of Miami, School of Medicine, Miami, Florida

Objectives: The specific aim of this research project is to continue efforts to determine if DNA can function as a molecular marker to differentiate between bladder epithelium irreversibly initiated by carcinogen and bladder epithelium with reversible nonmalignant lesions. The main thrust of this research is to investigate the possibility of developing immunochemical techniques to study the DNA of the bladder epithelium of the dog exposed to the aromatic amines in vivo and under conditions that lead to eventual tumor formation.

Accomplishments: Covalent binding of the chemical carcinogens with resulting modifications of the DNA of the target cells is thought to be involved in triggering of the carcinogenic response. A methodology that would permit the detection and characterization of these modifications in structurally intact DNA would be of great value in determining their role in cancer induction.

We have demonstrated that antibody to intact single stranded DNA (s-DNA) obtained from *M. lysodeikticus* having a 72 percent G-C ratio and modified in vitro by N-acetoxy-N,2-fluorenylacetaide (N-acetoxy-AAF) followed by complexation in a 1:1 ratio with methyl bovine serum albumin (MBSA) could be raised in rabbits. The antiserum obtained was shown to contain antibody that was capable of detecting carcinogen modified s-DNA in the presence of unmodified s-DNA by means of microcomplement fixation. This antisera also reacted with s-DNA modified in vitro by N,2-fluorenylacetaide (AAF) in the presence of phenobarbital stimulated rat liver microsomes and by N-hydroxy-N,2-fluorenylacetaide (N-hydroxy-AAF). The antisera produced against N-acetoxy-AAF modified s-DNA are directed to and specific for the AAF molecule covalently bound to the s-DNA.

These antibodies failed to react with *M. lysodeikticus* s-DNA reacted in vitro with N-acetoxy-N,4-biphenylacetaide or N,4-biphenylacetaide in the presence of phenobarbital stimulated rat liver microsomes and further demonstrated that the antibody produced was directed to the bound carcinogen. A radio-immunoassay has been recently reported that employs antibody against N-(guanosinyl-8-yl)-2-acetylaminofluorene (G-8-AAF) the major modified base formed when DNA is reacted with the N-hydroxy-AAF. The G-8-AAF was detected in the DNA of mouse and human cells exposed to N-acetoxy-AAF in vitro and in calf thymus DNA reacted in vitro with N-hydroxy-AAF and confirmed our observations. Our studies demonstrated that the antibodies produced against our modified intact s-DNA were specific for the carcinogen molecule bound to the DNA and not against some structural change in the DNA molecule itself. At this point, it became obvious that the development of an immunochemical method using antibody against carcinogen modified DNA as a probe to study modifications of nucleosome structure would require the DNA to be in a more structurally intact state. Therefore, we set out to determine at what level of structural complexity could the DNA be modified by a carcinogen and still be an effective immunogen that would yield antibody of sufficient titre and specificity to allow one to detect carcinogen modified DNA from unmodified DNA.

Program Director: William E. Straile, Ph.D.

Dog liver chromatin was isolated and the chromosomal non-histone-protein-DNA complex was prepared by the methods of Hnilica and co-workers. The non-histone-protein-DNA complex was then modified by reaction with N-acetoxy-AAF. This carcinogen modified DNA complex was then used to immunize rabbits following the schedule described by Spelsberg and co-workers. The antisera was decomplemented by heat and the globulin fraction obtained by DEAE-cellulose chromatography. At the present time, we have found that this antisera can detect the presence of N-acetoxy-AAF modified nonhistone-protein-DNA complex in the presence of unmodified complex using microcomplement fixation. This antisera does not react with s-DNA obtained from dog liver and reacted in vitro with N-acetoxy-AAF but does react with dog liver chromatin modified by this carcinogen. Recently, antibody to native calf thymus native DNA modified in vitro by N-acetoxy-AAF was prepared by Leng and co-workers. However, the antibodies they obtained react with both single and double stranded DNA and showed that the antigenic determinant is the d-GMP-AAF residues.

Plans: We are now in the process of studying the reactions of this antiserum with various preparations of dog liver DNA, representing various levels of complexity. Our preliminary data would seem to hold out the promise that antibody to a structural determinant induced by the carcinogen in the DNA structure, rather than one in which the carcinogen itself takes part, might be possible.

From: 01/01/75 to 21/31/83

FY 81: \$69,366

Dr. Frederick DeRubertis, Veterans Administration Hosp., Pittsburgh, PA 15420

Objectives: 1) To define the roles of cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP) and local prostaglandins (PGs) in the control of proliferation of normal colonic epithelium and in expression of colonic carcinogen action; 2) to examine the role of the PG synthetase system as a pathway for local metabolism and activation of procarcinogens by colonic mucosa; and, to examine the effects of diets of different lipid composition on PG synthetic activity in colonic epithelium, and the capacity of the tissue to metabolize carcinogens after PG synthetic activity is altered as a function of diet.

Accomplishments: Cyclic nucleotide metabolism was compared in normal rat colonic epithelial cells with different proliferative activities. Exogenous cAMP and agents such as vasoactive intestinal peptide, which increase endogenous cAMP in colonic epithelium, inhibit [³H] thymidine incorporation in short-term cultures of explants of rat and human colonic mucosa. By contrast, exogenous cGMP and agents which increase endogenous cGMP in colonic mucosa did not suppress [³H] thymidine incorporation. These findings indicate that cAMP acts to suppress proliferative activity of normal colonic epithelial cells. Intrarectal administration of a single-dose of DMH resulted in initial suppression of proliferative activity of distal but not proximal colonic mucosa, as reflected by a reduction in [³H] thymidine incorporation *in vivo*. This suppression was not associated with any detectable change in cAMP or cAMP-dependent soluble protein kinase activity and thus implied that it was mediated by a cAMP-independent pathway. However, an increase in proliferative activity of distal mucosa associated with a significant decline in cAMP and cAMP-dependent protein kinase activity in this region of the colon occurred within 3 days after DMH exposure. These results suggest that the reduction of cAMP after DMH may play a role in the enhanced proliferative activity of colonic epithelium induced by this carcinogen. We explored the possibility that PG synthesis and carcinogen metabolism were linked in colonic mucosa. Exogenous arachidonic acid (AA) markedly stimulated prostaglandin E formation by slices of rat and human colonic mucosa and by microsomal fractions prepared from these tissues. Addition of AA to the microsomal preparations significantly enhanced conversion of the procarcinogen benzo (a) pyrene (BP) to oxidation products which bind co-valently to DNA and protein. This action was suppressed by the PG synthetase inhibitor indomethacin and was abolished by O₂ deprivation, but was not enhanced by NADPH or inhibited by the microsomal oxidase blocker, 7,8-benzoflavone. By contrast, metabolism of BP by liver microsomes was dependent upon addition of NADPH and markedly suppressed by 7,8-benzoflavone, but was not inhibited by indomethacin. These results indicate that carcinogen metabolism by colonic mucosa is at least in part linked to the PG synthetic pathway and markedly enhanced by AA.

Plans: We plan to examine the role of AA-dependent, PG-linked cooxidation as a possible pathway for the local metabolism of other carcinogens, including DMH, by rat and human colonic mucosa *in vitro*. We plan to examine in rats the influence of dietary lipid (high vs. low unsaturated fatty acid; high vs. low cholesterol on membrane lipid composition in colonic mucosa, the capacity of this tissue to synthesize various PGs and the capacity of the tissue to metabolize carcinogens via a

Program Director: Vincent J. Cairoli, Ph.D.

co-oxidation pathway linked to PG synthesis as a function of diet. These studies may provide important new insights into the mechanisms by which dietary fat intake influences the development of colon cancer.

Publications:

DeRubertis, F.R. and Craven, P.A.: Cyclic Nucleotides in Carcinogenesis: Activation of the Guanylate Cyclase-cyclic GMP System by Chemical Carcinogens. Advances in Cyclic Nucl. Res., 12:97-109, 1980.

Craven, P.A. and DeRubertis, F.R.: Fatty Acid Induced Drug and Carcinogen Metabolism in Rat and Human Colonic Mucosa: A Possible Link to the Association of High Dietary Fat Intake and Colonic Carcinogenesis. Biochem. Biophys. Res. Comm., 94:1044-1051, 1980.

DeRubertis, F.R. and Craven, P.A.: Early Alterations in Rat Colonic Mucosal Cyclic AMP Metabolism and Protein Kinase Activity Induced by 1,2 Dimethylhydrazine. Cancer Research, 40:4589, 1980.

From 09/01/74 to 05/31/83

FY 81: \$143,415

Dr. Patrick C. Walsh, Professor and Director, Department of Urology, The Johns Hopkins University School of Medicine, 601 N. Broadway, Baltimore, Maryland 21205

Objectives: This study proposes to investigate the relationship between various target organ biochemical events and the biological behavior of prostatic cancer. Specifically, we propose to determine whether the measurement of steroid receptor content (androgen, estrogen, progesterone) steroid content (testosterone, dihydrotestosterone, 3 -androstenediol) or enzymatic profiles will be useful in predicting: (1) the quality and duration of response to hormonal therapy in men with metastatic prostatic cancers; (2) the response to chemotherapy in men with relapsing prostatic carcinoma; and (3) the disease free interval in men following radical prostatectomy.

Accomplishments: In order to assess whether pretreatment prostatic androgen receptor measurements would be of value in predicting the response to hormonal therapy in patients with prostatic cancer, 23 men with metastatic carcinoma of the prostate underwent prostatic biopsy prior to treatment. Cytosolic and nuclear prostatic androgen receptor content was measured by a single saturating dose, dextran-charcoal assay. All patients had measurable levels of androgen receptor in prostatic tissue and all demonstrated objective evidence of improvement following hormonal therapy. Thus, if androgen receptor measurements are to be useful in predicting prognosis, correlations between quantitative levels of receptor and quantitative aspects of response must be established. In this study response was quantitated by measuring the duration of both response and survival following hormonal treatment. The strong correlation between duration of response and survival ($p < 0.01$) demonstrated in this study suggests that survival in these patients is related directly to the duration of time patients respond to hormonal therapy. Neither total cellular nor cytosolic androgen receptor content correlated with response. However, nuclear androgen receptor content correlated with both the duration of response and survival following hormonal treatment ($p < 0.05$). Furthermore, in patients with nuclear receptor levels of < 110 fmol/mg DNA, the duration of response (7.1 ± 3.8 months) and survival (14.4 ± 5.9 months) were significantly shorter than in patients with higher levels of nuclear receptor (17.3 ± 10.4 and 24.7 ± 8.8 months respectively, ($p < 0.05$). These findings, which are the first report of a correlation between nuclear androgen receptor content and hormonal responsiveness, suggest that measurements of nuclear receptor may aid in identifying those patients unlikely to obtain a prolonged response from hormonal therapy.

Plans: Based on these studies, the measurement of androgen receptor content alone does not appear to be sufficient to predict prognosis in prostatic cancer. Indeed, it is possible that no single factor (receptor, enzymatic activity, enzyme index, steroid content) will prove useful and that ultimately multiple discriminatory functions will be required before a valid prognostic indicator is identified. With this idea in mind, we plan to pursue the development of microassays for the measurement of these parameters and to correlate these results with clinical aspects of response.

Program Director: Andrew Chiarodo, Ph.D.

Publications:

Murphy, J.B., Emmot, R.C., Hicks, L.L., and Walsh, P.C.: Estrogen Receptors in Human Prostate, Seminal Vesicle, Epididymis, Testis and Genital Skin - A Marker for Estrogen Responsive Tissues? J. Clin Endocrinol: 50:938-948, 1980.

Trachtenberg, J., Hicks, L.L. and Walsh, P.C.: Androgen and Estrogen Receptor Content in Spontaneous and Experimentally Induced Canine Prostatic Hyperplasia. J. Clin. Invest. 65:1051-1059, 1980.

Hawkins, E.F., Trachtenberg, J., Hicks, L.L. and Walsh, P.C.: Androgen and Estrogen Receptors in the Canine Prostate. J. of Androl. Vol. 1, No. 5: 234-243, 1980.

Trachtenberg, J., Hicks, L.L., and Walsh, P.C.,: Methods for the Determination of Androgen Receptor Content in Human Prostatic Tissue. Investigative Urology 18:349-354, 1981.

Fichman, K.R., Nyberg, L.M., Bujnovszky, P., Brown, T.R., and Walsh, P.C.: The Ontogeny of the Androgen Receptor in Human Foreskin. J. Clin. Endocrinol. and Metabolism. (In press).

From 09/01/74 to 08/31/81

FY 81: 0 (Ann. \$62,407)

A. J. Pesce, Ph.D., University of Cincinnati, Cincinnati, Ohio

Objectives: The most important progress of our work is our successful studies on B₂-microglobulin. This antigen can be considered as a possible model for the studies proposed for the urothelium specific bladder antigen. Several facts relating to this cell surface antigen component were uncovered (1) for a wide range of tumors, the tumor content of B₂-microglobulin is correlated with growth rate; (2) for the tumors tested there was a correlation between susceptibility to chemotherapy and B₂-microglobulin content; (3) the B₂-microglobulin released into circulation in an animal model correlated with tumor content and tumor mass; (4) variances in B₂ content could be correlated by immunohistology; (5) variances in B₂-microglobulin could be seen in human tumors by immunohistology, and we believe this is the first proof of the pleomorphic nature of human tumors. These data give strong credence to our proposal that organ-specific antigens should yield important biological data.

Accomplishments: Until recently, we had not found circulating immune complexes in bladder cancer patients; however, Dr. Terry Phillips and his colleagues at Georgetown had observed such complexes. We collaborated with Dr. Phillips and used four techniques to establish the existence of these complexes. Briefly, in this work we showed that patients from two different medical centers had circulating immune complexes. Four methods were used: polyethylene glycol precipitation, double crossed-immunoelectrophoresis, Raji cell and Clq binding assays. In the first group of 24 patients, 17 were positive for pathologically defined tumors of the serum sampled as judged by cystoscopy. Two tested positive for the presence of circulating immune complexes by all four techniques, and an additional one by three of the four techniques. In the second group of 54 sampled (41 of which had pathologically definable tumors at sample date), 9 were judged possibly positive by the Raji cell assay, the polyethylene glycol, and double crossed-immunoelectrophoresis techniques. When tested by the Clq binding assay, 8 of the 9 were positive, most being in the range of 260-320 ug/ml of immune complex. Combining all the data from the 78 patients with bladder cancer, 10 were definitely positive by four techniques and an additional two were positive by three techniques. Our data indicated that a low percentage (13-15 percent) of patients with bladder cancer had circulating immune complexes. Of importance is that the complex as judged by our assay procedure, bound Clg, contain aggregated IgG and can be associated into antigen and antibody. Thus, the immune complexes are similar to those found in immune complex disease.

Plans: We have developed a unique approach to the study of tumor antigens. The importance of the B₂-microglobulin study is that it shows an antigen component common to almost every cell on the body which can be used to study the biology of cancer. Indeed, this should not be considered surprising since a considerable amount of information has been gleaned from another isoantigen, the ABH system (Weinstein, Alroy). Thus far, the use of organ- or cell-specific antigens to study tumor biology has been restricted to animal systems or to transplantation biology of the kidney antigens (Ahlmén). Clearly the approach here can be used to investigate the biology of bladder cancer.

Program Director: William E. Straile, Ph.D.

From: 01/01/75 to 06/30/81

FY 81: -0- (Ann. \$195,036)

Dr. D.P. Griswold, Jr., Southern Research Institute, 2000 Ninth Avenue South,
Birmingham, AL 35205

Objectives: It is clear from the wide differences in the chemotherapeutic responsiveness of ten transplantable mouse colon tumors that no single tumor is a good predictive model for the other tumors or the human disease. This lack of "broadness" of activity of any clinically available or investigational agent, although unexpected for tumors of a single tissue type, does parallel treatment results of human colorectal cancers. Rarely is a given tumor responsive to two drugs. As a consequence of these observations, the fundamental focus of our studies has been the search for more broadly active single agents and combinations of agents.

Accomplishments: Although no single agent was found to be highly active against all of the transplantable colon tumors, seven investigational agents were identified that may be of value against human colorectal tumors. A new triazine antifolate (NSC 127755) was moderately to highly active against colon adenocarcinomas 36, 38, 10/A, and 12/A. A prolonged exposure at a low but effective concentration was necessary for optimum activity (e.g., 3x/day injections for 9 consecutive days). The combination of NSC 127755 plus vincristine (NSC 67574) was found to be potentiating against colon adenocarcinoma 10/A. Anthracenedione acetate (AA) (NSC287513) is slightly superior to dihydroxyanthracenedione (DioHA) (NSC 301739). Clinical trials are in progress in Europe and in the U.S.A. with AA and DioHA, respectively. Five potentiating combinations of anthracenedione were found. A more soluble nucleotide of 9- β -D-arabinofuranosyl-2-fluoroadenine (NSC 328002) was highly active against advanced-stage colon tumor 36 and was modestly active against an ara-C resistant subline of this tumor.

Plans: To improve treatment of large bowel cancer, we will continue to research for more broadly active investigational agents. In addition, practical sensitivity assays to identify agents that are active against each human tumor to be treated will be evaluated using the colon tumors for which in vivo drug responses are known. These include the Salmon-Hamburger assay and the Bogden subrenal capsule assay. We will explore the possibility that the responsiveness (or unresponsiveness) of a tumor to one agent (or class of agents) may signal responsiveness to some other agent. This approach may not only aid in the selection of an agent after treatment failure (or initial success), but may provide a better choice for combinations of agents that will increase the probability that both agents will be active against against a particular tumor.

Publications:

Corbett, T.H., Griswold, D.P., Jr., and Schable, F.M., Jr.: Activity of a New Triazine Antifolate (TA, 3-Chloro-4-[4-(4,6-Diamino-2,2-Dimethyl-S-Triazine-1 (2H)-yl) Phenyl] -Butyl-Benzenesulfonyl Fluoride with Ethanesulfonic Acid (1:1) (NSC 127755) Against Transplantable Mouse Tumors. Proc. Am. Assoc. Cancer. Res., 22:205, 1981.

Griswold, D.P., Corbett T.H., and Schabel, F.M.: Experimental Tumor Model for Evaluation of Imidazole-4-Carboxamide, 5- (3,3-Dimethyl-1-Triazeno) (DTIC) (NSC 45388). Proc. Am. Assoc. Cancer Res., 22:232, 1981.

Program Director: Vincent J. Cairolì, Ph.D.

From: 01/01/75 to 01/21/84

FY 81: \$60,377

Dr. William R. Brown, University of Colorado Medical Center, 1055 Clermont Street, Denver, CO 80220.

Objectives: The overall objective of our research is improved understanding of the immunobiology of the gastrointestinal tract, especially with respect to chronic inflammatory bowel disease and colonic carcinoma.

Our current research is directed towards understanding the cause and significance of the altered polar distribution of carcinoembryonic antigen (CEA) and secretory component (SC).

Accomplishments: We have demonstrated by immunocytochemical techniques that the normal polar surface distribution of two glycoproteins is abnormal in colonic carcinoma cells. SC normally restricted to the basolateral plasma membrane is reduced in amount or absent; CEA normally restricted to the apical plasma membrane, is expressed over the entire cell surface. We are using an animal model to study the abnormal distribution of surface membrane components in neoplastic transformation of colonic epithelial cells. Rabbit antiserum has been prepared to crude scrapings from the luminal surface of rat colonic mucosa. Antibodies specific for antigens restricted to apical surfaces of the colonic epithelial cells are purified from the antiserum. The animal model is being used to determine how surface membrane alterations occur during chemically induced carcinogenesis.

SC is expressed on the basolateral surfaces of the well-differentiated HT-29 human colonic carcinoma cells. Experiments on how this restricted surface expression of SC is established and maintained have begun. Surface and internal radiolabeling of SC is underway in order to determine the molecular sizes of SC associated with the cytoplasm, the plasma membrane, and secretions of the cells.

It is anticipated that techniques currently under study will be applied to investigate the determinants of the surface expression of glycoproteins on colonic epithelial cells. The synthesis and brush border insertion of amino oligopeptidase in rat small intestine has been studied and is found to be synthesized as a single 130,000-dalton polypeptide chain.

Plan: We will continue research on the synthesis and external expression of glycoproteins by isolated or cultured colonic epithelial cells, on the development of an animal model for altered surface glycoproteins, and on use of the animal model in the therapy of experimentally induced colonic carcinomas.

Publication: Ahen, D.J., Nakane, P.K., and Brown, W.R.: Ultrastructural Localization of Carcinoembryonic Antigen in Normal Intestine and Colon Cancer. Abnormal Distribution of CEA on the Surfaces of Colon Cancer Cells. Cancer, in press, 1981.

Program Director: Vincent J. Cairolì, Ph.D.

From 05/01/75 to 06/30/82

FY 81: \$322,625

Dr. T. Phillip Waalkes, Comprehensive Cancer Center, Johns Hopkins University, 601 North Broadway, Baltimore, Maryland 21205

Objectives: This grant provides essential support for overall Program development, planning and review. Three primary elements are involved: (1) Core support for key staff members and for members of the Johns Hopkins Cancer Control directorate. The latter group, with expertise and diversified backgrounds in Cancer Control, have responsibility for program planning, development and evaluation. (2) Professional Education for community physicians, nurses and allied health professionals; and (3) Developmental projects which are initiated as feasibility demonstration studies, reviewed and evaluated as possible regional community projects for further implementation and subsequent evaluation. Associated with the latter are specific plans for appropriate data acquisition for evaluation purposes.

Accomplishments: Over the past year and a half of the grant period the Cancer Control Directorate has met an average of once a week to once in two weeks. In addition to overview of the existing program, the Directorate reviewed and approved ten Cancer Control projects in the developmental category. Prior to consideration for implementation all such projects were extensively reviewed by specific protocol format which included objectives, methods of procedure, and plans for evaluation. These projects were: (1) Johns Hopkins Employee Cervical and Breast Cancer Detection Program and a Breast Self-Examination Education and Demonstration Program; (2) Factors in Rehabilitation; (3) Multidisciplinary Discharge Planning; (4) Patient Health Education; (5) Smoking Cessation Demonstration; (6) Home Care; (7) Feasibility Program in Community-Center Clinical Data Systems; (8) Development of Targeted Public Education Protocols; (9) Development of Community Hospital Cancer Programs; and (10) Community Network Clinical Evaluation Program. In addition, the Cancer Control Directorate has given major attention to the requirement of essential organizational planning on a regional basis in Maryland for the proper implementation and evaluation of priority Cancer Control Programs meeting defined needs within these regions.

Professional education has been a major effort of the Oncology Center's Community Outreach Program. Assistance and participation in the development of Community Hospital continuing professional education programs for physicians has been given in 18-20 hospitals throughout the State. In addition, educational programs involving community physicians include: (1) participation in the Center's outpatient clinic; (2) specific clinical protocols developed jointly by Community-Center Physicians; (3) an annual course in various aspects of neoplastic diseases for community physicians; (4) an annual course in gynecologic malignancies; (5) a bimonthly Community-Center Physicians' meeting to discuss problems or interesting patients; (6) a weekly multidisciplinary conference; and (7) the Center's weekly Grand Rounds to which community physicians are invited. Prior to the Center's Cancer Control Program, essentially no Nursing Education Programs existed in Maryland. The Center's Community Nurs-

Program Director: Carlos E. Caban, Ph.D.

ing Professional Education Coordinator has subsequently established six regional areas in Maryland (in collaboration with local hospitals, ACS, and community colleges) through which specific and continuing oncologic nursing education programs are provided. In addition, approximately 20 community nurses have participated in the individual training program in oncology at the Center as part of the Developing Cancer Network plan. Similarly, workshops and individual training at the Center and in Network Community Hospitals has been provided to aid in the appropriate development of Cancer Programs, and specifically essential data systems or registries.

Plans: Plans for the Oncology Center's Cancer Control Program, for the core faculty and staff, and for the Cancer Control Directorate, will continue to focus on (1) review, development and evaluation of specific intervention projects which will be most meaningful in response to perceived, documented community needs; (2) network regional organizational plan to assure maximum effectiveness of the total Cancer Control Program in Maryland; (3) targeted professional education programs, based on a proposed, objective, clinical evaluation plan; and (4) appropriate data collection and systems development to enhance and assure essential program evaluation.

Publications:

Aplasia and Infection Control: Information for Patients, Baltimore, Md., 1980, 66pp.

Your Chemotherapy Medications, Baltimore, MD., 1979, 18pp.

Your Child's Chemotherapy Medication, Baltimore, MD., 1979, 15pp.

Elwood, T.W., Waalkes, T.P., and Vaughn, W.P.: (Ed.) Health Education Perspectives of the 80's, Nine Case Studies. In press. 1981.

From: 06/01/75 to 05/31/84

FY 81: \$78,844

Dr. Sherwood L. Gorbach, Tufts University School of Medicine, 171 Harrison Avenue, Boston, MA 02111

Objectives: The goals of our research project are directed at evaluating the effect of diet, antibiotics, and oral bacterial supplements on the metabolism of carcinogens. Specifically, we are interested in the role of the intestinal microflora in metabolic alteration of procarcinogens. We plan to suppress the microflora enzymes by diet, antimicrobial agents, and *Lactobacillus* supplements and to alter the microflora of volunteers in a benign manner with *Lactobacillus* supplements and tetracycline.

Accomplishments: Previous experiments indicated that high fat diets increased the reduction of nitro-naphthalene to naphthylamine. The opposite effect was noted when animals were given greater than 10^{10} *Lactobacillus acidophilus* daily. These experiments were repeated using either 10 mg per day of erythromycin or 10^9 *Lactobacillus* per day as the intestinal bacterial perturbant. This level of *Lactobacillus* corresponds to the amount of organisms that would be consumed in drinking 500 ml of commercially available acidophilus milk. Both treatments caused a significant decrease in the reduction of nitro-fluorene (20 mg in a single oral bolus) to aminofluorene. In a separate experiment, twenty-one volunteers were given 10^9 *Lactobacillus* in 500 ml of milk daily, the equivalent of consuming two glasses of acidophilus milk. Fecal specimens were collected every ten days over a 150 day period. The experiment was divided into five periods each consisting of three collections. Fecal β -glucuronidase, nitroreductase, and azoreductase were measured for each subject three times (10 days apart) in the initial baseline period (baseline 1). The collections and assays were then repeated after administering 500 ml of milk not containing an additional bacterial supplement. A second baseline was then taken followed by giving subjects 500 ml of milk containing 10^9 *L. acidophilus* followed by a final baseline period (baseline 3). The results showed that milk did not cause a decrease in fecal bacterial enzyme activity. However, the milk containing *L. Acidophilus* did cause a significant decrease in all three bacterial enzyme levels. All three enzyme activities significantly increased during the baseline 3 period. These results indicate that alteration of the intestinal microbial environment by *L. acidophilus* is transient.

Plans: Studies are planned in animals after their flora has been altered by diet, antibiotics and bacterial supplements. The kinetics and distribution of carcinogen metabolites will be evaluated to determine to what degree the natural intestinal flora participate in the metabolism of carcinogens. We have developed a reliable assay to detect fecal mutagens after feeding nitrofluorene, aminofluorene, and aminofluorene - β -glucuronide. Work is now in progress to determine the effect of antibiotics and *L. acidophilus* on fecal mutagen excretion after oral administration of a procarcinogen.

Publications:

Goldin, B.R. and Gorbach, S.L.: The Effect of Antibiotics on the Incidence of Intestinal Tumors in Rats Induced by 1,2-dimethylhydrazine. J. Natl. Cancer Inst., in press.

Program Director: Vincent J. Cairoli, Ph.D.

Grant 17559: Investigations on Prostate Adenocarcinomas in Rats

From 05/01/75 to 08/31/84

FY 81: \$85,810

Dr. Morris Pollard, Lobund Laboratory, University of Notre Dame, Notre Dame, Indiana 46556

Objectives: Since the etiology and pathogenesis of prostate cancer in man is obscure, we resort to the development and study of model tumor systems in experimental animals. Germfree aging Lobund-Wistar rats developed metastasizing prostate cancer "spontaneously". Several lines of tumor cells have been propagated by in vivo and in vitro procedures to analyze the unique characteristics of the cells, host-tumor interactions, and factors responsible for the phenomenon of metastasis.

Accomplishments: Four distinct lines of prostate adenocarcinomas have been developed: three metastasize through lymphatic channels to the lungs; and a fourth line spreads through lymphatic and blood channels to multiple visceral organs plus bone marrow. Metastasis has been accelerated by administrations of phenobarbital and heparin, and retarded by administrations of prostaglandin-blocking agents. The action of heparin has been related to destruction of very low density lipoprotein (VLDL) which has a demonstrable protective (oncolytic) action. A very high level of plasminogen activator and other fibrinolytic agents are produced by the prostate cancer cells which may be related to the process of metastasis. The tumor cells have been used for screening anti-cancer drugs (Cyclophosphamide, ICRF-159, VLDL, interferon) by in vitro and in vivo procedures. A procedure has been developed for delayed release of anti-cancer drugs which avoids the necessity for repeated administrations of drug. The results have been reported at symposia in Tokyo, Peking, London, and Paris.

Plans: We plan to further define the relationship of metastasis to the high levels of fibrinolytic enzymes produced by the prostate tumor cells; and methods for interfering with metastasis. We will test additional anti-tumor agents, using the prostate tumor cells for screening by in vivo and in vitro procedures. Since the Lobund-Wistar rat is unique in its susceptibility to metastasizing prostate adenocarcinomas, we plan to study this rat strain further for factors which contribute to this disease.

Publications:

Articles Published in a Periodical:

Pollard, M.: Animal Models for Prostate Cancer. The Prostate 1: 207-213, 1980.

Chan, S-Y and Pollard, M.: Metastasis Enhancing effect of Heparin and its Relationship to a Lipoprotein Factor. J. Natl. Cancer Inst. 64:1121-1125, 1980.

Program Director: Andrew Chiarodo, Ph.D.

Chan, S-Y: Androgen and Glucocorticoid Receptors in the Pollard Prostate Adenocarcinoma Cell Line. The Prostate 1: 53-60, 1980.

Jenis, D.M., Basu, S., and Pollard, M.: Increased Activity of (β 1-4) Galactosyltransferase in Tissues of Rats Bearing Prostate and Mammary Adenocarcinomas. Cancer Research 1981, in press.

Pollard, M., Burleson, G.R., and Luckert, P.H.: Interference with in vivo growth and metastasis of prostate adenocarcinoma (PA-III) by ICRF-159. The Prostate 2: 1981, in press.

Articles Published in a Book:

Pollard, M., Teah, B.A., and Luckert, P.H. The Development of Tumor Model Systems in Germfree Rats. In Flidner, Heit, Niethammer (Eds.): In Clinical and Experimental Gnotobiotics. Stuttgart, Gustav Fischer Verlag, 1979, pp. 321-324.

Pollard, M.: The Pollard Tumors. In Murphy, G.P. (Ed.): Models for Prostate Cancer. New York, A.R. Liss, 1980, pp. 293-302.

Pollard, M.: Metastatic Spread of Experimental Neoplasms. In Hellmann, K., Hilgard, P. and Eccles, S. (Eds.): Metastasis - Clinical and Experimental Aspects. The Hague, Nijhoff Publishers, 1980.

Grant 17806: Childhood Cancer: Psychosocial Rehabilitation

From 05/01/75 to 04/30/81 FY 81: 0 (Ann. \$149,941)
Dr. Shirley Lansky, University of Kansas Medical Center, 39th and
Rainbow Boulevard, Kansas City, Kansas 66103

Objectives: The objectives of this project are to study three areas which emerged as highly important to the integrity of the family in our previous research. These are: (1) Patients' compliance with oral chemotherapy (prednisone) and psychological factors involved in compliance; (2) the out-of-pocket costs of childhood cancer, both medical and non-medical; (3) the intellectual and academic status of children with cancer, with particular attention to those who receive prophylactic central nervous system treatment (irradiation and/or chemotherapy).

Accomplishments: Compliance - For the compliance study, we have completed the data collection on 35 patients, 24 mothers, and 25 fathers. Data analysis has been completed, and the report is being written. Cost of Illness - Data on monthly medical bills have been collected on 66 families. Forty-three of the 66 families returned the questionnaire regarding medical insurance deduction on federal income tax returns. For 15 children who died of cancer, we have total costs of illness and death. All of the above data is ready for computer analysis. Intellectual Academic - Fifty patients, 16 siblings, and 17 matched controls, have completed two test batteries. Additional data on this sample include school records, CAT scans and neurological exams. The data analysis is underway.

Plans: In the final phase of the project, we will be completing the data analysis on the cost-of-illness data, and on the intellectual/academic study. Reports are being written on all three data sets.

Publications:

Cairns, N.U., Clark, G.M., Black, J. and Lansky, S.B. Economics of cancer: financial impact on the family. In Childhood Cancer: Stress and Survival, C.V. Mosby Co., St. Louis, in press.

Lansky, S.B., and Cairns, N.U. Affective, Social and Cognitive Issues and Interventions. In Sutow, W., Vietta, T. and Fernback, D. (Eds.). Clinical Pediatric Oncology, St. Louis, C.V. Mosby Co., 1981, in press.

Smith, S., Cairns, N., Sturgeon, J., and Lansky, S. Poor drug compliance in an adolescent with cancer. J. of Pediatric Hematology/Oncology, 1981, in press.

Lansky, S.B. and Cairns, N.U. Cancer: The Patient and the Family. In Holder, T.M. and Ashcraft, K. (Eds.). Pediatric Surgery, Philadelphia, Pa., W.B. Saunders, 1980, Chapter 69, 923-931.

Program Director: Rosemary Yancik, Ph.D.

From 06/01/76 to 06/30/82

FY 81: \$220072

Dr. John E. Healey, Jr., Comprehensive Cancer Center for Florida,
University of Miami, Coral Gables, Florida 33124

Objectives: To continue to update cancer control resources and facilities in the State of Florida; to assess cancer control needs at the State and local level; to disseminate the most current knowledge of cancer to health providers and the general public with the ultimate objective to reduce cancer incidence, morbidity, and mortality in the State of Florida.

Accomplishments: Legislative activities of the Cancer Control Core Staff have resulted in the formation of a Florida Cancer Data System (FCDS). Every hospital in the State of Florida must report information on all cancer patients on a standardized form by June of 1981. This statewide registry is supported by the Florida Department of Health and Rehabilitative Services and operated by the Comprehensive Cancer Center's Division of Biostatistics. The Director of the Division of Cancer Control was also instrumental in the passage of the Florida Cancer Control and Research Act. This Act requires that the Cancer Control and Research Advisory Board formulate a yearly Florida Cancer Plan to be submitted to the Governor. Center Staff and particularly Control Staff made significant contributions to the Plan. The Chairman of our Area #6 Cancer Control Committee was selected to serve as a liaison person between the Area Committee and the Board, so as to assure local input to the plan.

Updating of the Cancer Control Resource Directory was continued and a document, Florida Cancer Comments, was published. This document cites demographic data, cancer mortality rates by county, cancer resources and facilities, and information regarding Florida cancer legislation. Work has been completed on a third booklet, "Coping with Cancer": A Guide to Community Resources in North Central Florida.

Meetings were held with representatives of the University of Florida, University of South Florida and the University of Miami for planning a Florida Inter-University Cancer Education Program. In addition, in cooperation with the Florida Cancer Council, the American Cancer Society and the Florida division of the American College of Surgeons, planning meetings are being held to develop a Florida Hospital Cancer Management Program.

Other new projects which we have assisted in developing have been the Phillip Strax Breast Cancer Detection Clinic in Broward county, the Cervical Cancer Detection Clinic and the Thyroid Cancer Detection Clinic at Jackson Memorial Hospital Clinic and the Cancer Detection Clinic at the Pasteur Clinic.

The Control staff also has been deeply involved in the Florida Pediatric Tumor Program, a network of eight hospitals within the State. A staff member serves on their Board of Directors and the control staff members serve as evaluators of the program.

Program Director: Carlos E. Caban, Ph.D.

We have been unable to implement the affiliative program for training oncology fellows from the Puerto Rico Cancer Center because of lack of funds.

Plans: We hope to implement both the Florida Inter-University Cancer Education Program and the Florida Hospital Cancer Management Program within the next year, through State or private funding. Other plans are dependent upon future funding.

Publications: Healey, John E., Jr.: Florida Cancer Comments; Miami, Florida, University of Miami Press, 1980, 83 pp.

Coping with Cancer: A Guide to Community Resources in North Central Florida. Miami, Florida, University of Miami Press, 1981, 87 pp.

From 07/01/75 to 07/01/85

FY 81: \$112,048

Dr. Peter W. A. Mansell, University of Miami School of Medicine,
Miami, Florida 33101

Objectives: The program provides cancer education for medical students at the University of Miami School of Medicine, for interns and residents and Jackson Memorial Hospital, University of Miami Hospitals and Clinics and the Veterans Administration Hospital in Miami and for post residency oncology fellows in the departments of Medical, Surgical, Gynecological and Radiation Oncology. Education is also provided for doctors, dentists and pharmacists, and through our nursing program for nurses and LPN's, throughout the state of Florida. Public education is also becoming integrated into the program. The medical student and nursing curricula at the University of Miami Medical School and Nursing School will have increasing emphasis on cancer education. Teaching materials in the form of texts, films and audiovisual tapes are being developed to complement the various curricula. Senior medical student electives and resident electives will be encouraged in the Department of Medical Oncology as well as the other oncological departments throughout the University. The entire emphasis of our educational programs is multidisciplinary and this will continue to be developed.

Accomplishments: The accomplishments of this program are many and include the development and continuation of an undergraduate curriculum in cancer education given during the sophomore year. This course, which lasts two weeks, in generally exceedingly highly rated by the students. In the course of the development of this program, a text has been written which is updated every year and distributed free to every medical student. The Ph.D. to M.D. program similarly has a short but intensive program of cancer education which has increased in length and quality over the past several years. An increasing number of senior medical students are choosing medical oncology as an elective and this trend is being encouraged as much as possible through contacts with the student body. In graduate education, the center continues to be involved in statewide cancer education for medical practitioners and nurses and to support education and training for interns, residents and post-residency fellows at the University of Miami School of Medicine. Through our liaison with the two other medical schools in the state, at Gainesville and Tampa, cancer education in those schools is being increasingly emphasized. Our programs of Grand Rounds, Journal Clubs, Tumor Boards, Research Seminars and the Visiting Speaker program, although the latter has been drastically curtailed recently, continue to appeal to a wide multidisciplinary audience throughout the University and the Medical School. The Biology of Cancer course for undergraduates at the main campus has now been given for a third year and is generally judged to be an extremely successful and worthwhile course by the audience and the participants. Educational programs for tumor registrars and the clergy have been given again this past year and will continue to be a feature of our program in the future.

Plans: Our plans are to continue and expand our present activities and to undertake a number of new programs in the immediate future. These will deal with 1) school education in Dade County; 2) health education for the elderly through United Way and the related agencies; 3) an educational program at the School of

Program Director: Margaret H. Edwards, M.D.

From 07/07/75 to 06/30/83 FY 81: \$57,364
Dr. Sol Silverman, Jr., University of California, San Francisco
Dental School, San Francisco, California 94143

Objectives: This education program is designed to maximize for dental students, practitioners, and other professionals their capabilities in oral cancer recognition, diagnosis and management.

Accomplishments: Undergraduate dental teaching hours in cancer have been increased, with one entire quarter of the second year (50 hours) being entirely oriented to oncology (108 dental students, 29 dental hygiene students). Lectures on oral cancer are also given to medical, nursing and pharmacy students.

Special instruction and cancer patient presentations are made weekly for 18 rotating third year students (10 hour - 5 week rotations).

At weekly multidisciplinary head-and-neck pre-treatment conferences (ENT, Radiation Oncology, Medical Oncology), dental participation includes a minimum of four faculty and three undergraduate and/or postdoctoral students. Additionally, weekly one-hour hospital rounds for inhouse head-and-neck cancer patients have been instituted (organized by our social worker).

There is a fully functioning teaching and service maxillofacial cancer rehabilitation unit. There is weekly faculty coverage in the Oral Medicine Clinic for consultations regarding diagnosis, treatment evaluations and rehabilitation for cancer patients.

Two clinical associates were supported for their educational experience this year.

Plans: With the cancer patient volume that is now being seen in the Oral Medicine Clinic (over 200 new patients each year and over 2,000 patient visits), a large pool of data is being collected, computerized and programmed for analysis and characterization.

A comprehensive and fully illustrated oral cancer monograph, partially supported by this grant, is presently being printed for national distribution.

A General Practice Residency Program, under the direction of Oral Medicine, is being increased to eight residents a year. As a part of their training they will have an intensive head-and-neck oncology program.

Educational programs for community dentists, physicians and other professionals are planned at least monthly to continually re-emphasize the importance of early detection, multidisciplinary treatment, and participation in rehabilitation efforts.

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Taped programs on various aspects of cancer are being planned, as well as a comprehensive quiz for knowledge assessment.

A hygienist will be hired to increase the role of the dental hygienist in patient service, teaching and counseling.

From 07/01/78 to 06/30/84

FY 81: \$77,571

Dr. Robert M. Beazley, Louisiana State University Medical Center,
New Orleans, Louisiana 70112

Objectives: The objective of this Cancer Education Grant Program was to aid in the evolution of a multidisciplinary cancer education program at the three levels of professional development, preclinical and clinical medical students, the postgraduate trainee, and the practitioner in continuing education.

Accomplishments: Over the three years of Cancer Education Grant activity at the Louisiana State University Medical Center, a number of changes have resulted. Firstly, pre-clinical cancer education has been more formalized with eight multidisciplinary hours of oncology lectures being given to the sophomore class. In addition, the Cancer Education Committee has been able to influence individual Departments to increase oncology related materials such as Death and Dying, Cancer Chemotherapeutic Agents and Nutrition. Clinical assistantships have been offered each summer with a total of twenty-eight students being exposed to laboratory or clinical cancer projects over the three years. Three of these students have worked in epidemiology programs in Louisiana exploring Lung and Pancreatic Cancer. The Departments of Pathology, Hematology Oncology, Pediatrics, Surgery, and Immunology have all had clinical assistants at one time or another. A number of publications have resulted directly or indirectly from students' work.

Visiting consultants are available due to support from this grant. The visiting consultants have generally spent at least one day and a number have spent several days in the Medical Center consulting formally and informally with faculty and students.

On the graduate basis two clinical associates have been funded by the Cancer Education Program, one in Pediatric Oncology, and one in Medical Oncology. As a result of the Pediatric Oncology Associate an affiliation has developed with the Ochsner Foundation Pediatric Oncology Department which should have a long-lasting and wide-spread impact on the community. The presence of the Medical Oncology Associate has helped to stimulate the development of the first bone marrow transplantation program in Louisiana. Both associates have participated extensively in student teaching and resident training.

Lastly, in continuing education, two major seminars had been given with attendance in the range of approximately 200 practitioners and national consultants. In May, 1979 the topic of breast cancer was discussed in a day-long seminar which included Dr. Byrd, Dr. Carlile, Dr. Black, Dr. Donengan, Dr. Lerner, and Mrs. Rose Kushner. Likewise in February 1980, a faculty of very similar national stature presented a program entitled "new Dimensions in Colorectal Cancer". Both of these programs were well received in the local community.

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Lastly, the Clinical Cancer Education Grant has indirectly influenced a broad spectrum of oncologic activities in the Medical Center. Establishment of the grant subsequently led to the development of the section of Surgical Oncology with recruitment of additional faculty and the award of an American Cancer Society Clinical Professorship to the Medical Center. It is unlikely that this would have occurred had the Clinical Education Grant not been in place.

Plans: Plans for the coming year include continuation and broadening of undergraduate education as well as the clinical assistants' program aimed primarily at the freshman class; continuation of the Medical Oncology and a joint Pediatric Oncology Program with the Ochsner Clinic; the development of a Clinical Oncology Library Service as well as the development of a Master's program in Oncology Nursing within the nursing school; and development of an "outreach program" of Tumor Conferences which would reach the practicing physician in his community in the area within 60 to 80 miles of the New Orleans Metropolitan Area.

From 06/30/76 to 06/30/81

FY 81: 0 (Ann. \$88,815)

Dr. C. E. Butterworth, Jr., University of Alabama, 800 South 16th Street,
Birmingham, Alabama 35294

Objectives: To develop and evaluate the effectiveness of aggressive nutritional support in extending limits of tolerance to conventional cancer therapy. A closely related goal has been to rehabilitate cancer patients whose nutritional state has been compromised by successful cancer management. The rationale of the project is that nutritional support will promote natural tissue repair and immune mechanisms. The significance is that improved nutrition promises to improve cure rates, minimize non-cancer deaths, and improve the quality of life of cancer victims.

Accomplishments:

- a. During the year data have been gathered on 21 additional cancer patients who received specialized evaluation (consultation and management) by the Nutrition Support Team. Eight had no evidence of protein-calorie malnutrition. Of the remaining 13, 2 had marasmus, 3 had marasmic-kwashiorkor, and 8 had kwashiorkor. Only 2 of the 8 patients with kwashiorkor died, in contrast to our experience in the early phases of this project (1978-1979) at which time we reported a mortality rate of 75-80% in patients with kwashiorkor.

Although it is difficult to isolate the effect of other possible contributory effects we believe that early assessment of nutritional status combined with vigorous nutritional support has been a major factor in improving the survival rate in these patients.

- b. Routine assessment of nutritional status of cancer patients admitted to the metabolic unit of the cancer center and elsewhere is continuing. Computer programs have been developed and tested, to simplify the retrospective evaluation of these charts and correlation with outcome, or "performance." However, even the primary collection of information for computer storage has proven to be time-consuming and difficult. We have data in a related area, demonstrating that aggressive nutritional support of 35 burn patients significantly shortens the duration of hospitalization in comparison with 35 matched subjects who did not receive such support two years ago. It is anticipated that the analysis of data from cancer patients will reveal similar beneficial effects of nutrition support.
- c. A study has been completed in which all patients admitted to the metabolic unit of the Cancer Center during a 3-month period had detailed nutritional assessment in conjunction with on-going accession of data. Eighty-two sets of assessment data are available on 76 patients (6 repeats) including observations on 7 standard indices and 3 special tests. The purpose of the study was to determine if nutritional assessment could be simplified by making observations on nutrient-transport proteins with short half-lives: transferrin, transcobalamin II, and retinol-binding prealbumin.

Program Director: Lawrence D. Burke

A bivariate correlation matrix revealed that serum albumin correlated significantly with the greatest number of other parameters (weight loss, TSF, MAMC, total serum protein, and transferrin). Hence, the serum albumin concentration remains a valuable inexpensive, widely-available indicator of nutritional status in cancer patients.

A second phase of the study revealed data of equal or perhaps greater, usefulness. Five patients receiving cancer chemotherapy with adriamycin either alone or in combination with other agents had serial assessments of transferrin, transcobalamin II, and retinol-binding prealbumin. Measurements made at 8, 24, 48 and 120 hours after baseline revealed no decline in these transport proteins, some of which have a half-life of approximately 12 hours. Thus, if cancer chemotherapy patients develop depressed levels of serum iron, B12, or retinol, it is probably more appropriate to consider inadequate intake than impaired transport capacity.

- e. An analysis has been completed of nutritional assessment data from 100 consecutive cancer patients with regard to triceps skinfold (TSF), weight-for-height, absolute lymphocyte count, and serum albumin; delayed hypersensitivity skin-testing was done in 20 of these (see: Proceedings of the International Symposium on Clinical Nutrition, London, 1980). In brief, these studies demonstrate (1) considerable residual obesity (as also described by others) in cancer patients, (2) a very high prevalence of hypoalbuminemia (67% of this series had values 3.5 g/dl, (3) absolute lymphocyte counts and skin tests are of limited usefulness in this population.

Plans: We plan to complete the computer-assisted review of the course of illness in all available records from cancer patients who have had nutritional assessment data recorded, in relationship to nutritional support procedures and eventual outcome. We also plan to continue implementation of the diagnostic and support procedures developed under this grant, to make them more and more a routine part of the management of cancer patients.

Publications:

Hunker, Edith M. Nutritional Therapy for the Cancer Patient, in: Nursing Care of the Cancer Patient, 4th Edition. Rosemary Bouchard and Normal Owens, Editors, C.V. Mosby Company, 1981 (IN PRESS)

Hunker, Edith M. Nutrition Therapy for the Ostomy Patient, in: Ostomy Care, 1st Edition, Debbie Broadwell and Bettie Jackson, Editors, C.V. Mosby Company, 1981 (IN PRESS)

Hunker, F. D., Bruton, C. W., Hunker, E. M., Durham, R. M. and Krumdieck, C. L. "Metabolic and Nutritional Evaluation of Patients Supported with Mechanical Ventilation." Critical Care Medicine 8:628-632, 1980.

Butterworth, C.E. Jr. "Assessment of Nutritional Status With Particular Reference to Patients Hospitalized for Cancer." Chapter I in Recent Advances in Clinical Nutrition. (Proceedings of the International Symposium on Clinical Nutrition), Libby & Co., London, 1981 (IN PRESS)

Weinsier, R.L. and Butterworth, C.E., Jr. Handbook of Clinical Nutrition. C.V. Mosby Co., 1981

From 07/01/77 to 06/30/82

FY 81: \$62,527

Dr. Mario G. Martinez, Jr., The University of Alabama School of Dentistry,
Birmingham, Alabama 35294

Objectives: This program is designed to develop, promote and implement education programs on cancer of the head and neck, with the main goal of optimal patient care. The objectives will be accomplished through: 1) special, comprehensive, multidisciplinary educational programs for undergraduate, postgraduate, dental auxiliary students as part of the regular dental school curricula; 2) continuing education programs and special seminars for practicing clinicians, and 3) educational programs for the public to stimulate early diagnosis of cancerous lesions. Each of these programs will present basic knowledge of the biology, pathogenesis, diagnosis, prevention, and management of malignant diseases.

Accomplishments: (1) New topics on epidemiology, nutrition and oral cancer, psychosocial oncology, and basic tumor immunology were added to the undergraduate oncology courses. Special evaluation with pre-course test and post-course test were also established. (2) Special lectures on head-and-neck cancer for dental auxiliary personnel. (3) Development and implementation of a summer program on clinical oncology for junior and senior dental students (clinical assistants). (4) Development and implementation of a dental oncology postgraduate training program. Two individuals have been trained; the first trainee is in an Oral Surgery/M.D. training program, and the other, after two years of training, will stay in academic dentistry. (5) Development and implementation of the Dental Oncology Service of the School of Dentistry to serve the in-house and out-patients from the L. Wallace Comprehensive Cancer Center and Tumor Institute. (6) Development of special dental protocols for bone marrow transplant patients. (7) With the financial support of the administration of the School of Dentistry, the development of a faculty position for the Dental Oncology Service. (8) Seminars on oral cancer presented to: a) Residents and faculty of the General Practice Program; b) Residents and faculty in maxillofacial prosthodontics; c) Residents and faculty in the General Practice Program in the Huntsville program; d) Residents in E.N.T. program, and e) the staff of the Tuscaloosa Veterans Administration Medical Center. (9) Development and implementation of public education programs on prevention, early signs and symptoms, and diagnosis of oral malignancies. (10) Development and implementation of slide-tape instructional units on self-examination of the head and neck, and clinical manifestation of oral cancer for public use. (11) Results of the evaluation of most of our programs have been very favorable and they have been presented at the annual meetings of the AACE.

Plans: For the coming year 1981-82, we have programmed the following activities: 1) improvement of the clinical material on oral cancer presented to the undergraduate dental students; 2) implementation of short clinical research programs for clinical assistants during the summer programs; 3) with the new faculty position in charge of the Dental Oncology Service, the program and the patient care will be much better, and 4) the evaluation methodology for our programs will be more effective. In general, all aspects of our programs will be improved.

Program Director: Margaret H. Edwards, M.D.

Grant 17945: Sensory Feedback Leg Prosthesis for Cancer Patients

From 05/01/75 to 06/30/82

FY 81: \$176,430 (estimated)

Dr. Frank Clippinger, Duke University Medical Center, Department of Surgery,
P.O. Box 3935, Durham, North Carolina 27710

Objectives: Amputations performed for malignancy in lower extremities are usually at a high level (high above knee or hip disarticulation as opposed to those done for vascular or diabetic disease (low above knee or below knee). Without a knee joint to provide proprioception, the cancer amputee is at a great disadvantage in training for use of the traditional prosthesis.

Accomplishments: Reliability of units are now to an acceptable level for all patients. Emergency repairs have not been necessary and maintenance has taken place when patients return for sensory feedback clinic check-ups. We are now field testing a more durable and cosmetically acceptable cover. We have devised a system for evaluating the forces and moments at the knee during level walking. A normal control group has been studied and compared with a variety of amputees. A set of gait descriptors based on foot and knee forces and moments has been developed to evaluate level walking performance quantitatively.

Plans: The approach for this study is to utilize an electrical implant for peripheral nerve stimulation. Electrodes will be placed on peripheral nerves for control of pain. This study will also produce data on the long-term effects of peripheral nerve stimulation on stump pain and circulation problems. In addition, the existing patient population with implanted peripheral nerve stimulation present a unique opportunity to study sensory physical phenomena. These human implant studies, as well as animal experiments, have demonstrated no damage to nervous tissue secondary to pulse stimulation.

Program Director: Lawrence D. Burke

From 07/01/76 to 06/30/82

FY 81: \$119,037

Dr. Gene Ridenhour, Ellis Fischel Cancer Research Center,
Columbia, Missouri 65205

Objectives: The overall goal of the program is to improve the care of cancer patients by providing 1) education to graduates and undergraduates; 2) continuing medical education for health professionals and 3) patient education about cancer detection, diagnosis, treatment, rehabilitation and research. The complete management of all patient problems--clinical, emotional and psychosocial-- can be accomplished by a multidisciplinary approach to patient care. The importance of a properly informed patient and family is an emphasis integrated into the education program of the graduate and undergraduate students. Keeping abreast of the latest trends in cancer research, therapy or rehabilitation increases professionals' capacities to provide the best care possible. Semiannual professional programs conducted jointly by Ellis Fischel State Cancer Hospital and the Cancer Research Center bring in visiting professors to provide information on the latest knowledge or ideas in cancer research and patient care.

Accomplishments: 1) Clinical Training Program for three Clinical Associates in Radiation Therapy, Pathology, and Medicine and 60 Clinical Assistants in Surgery, Medicine, and Radiation Therapy. 2) Residency training program for University Missouri Medical School surgery residents and rotations for University of Missouri Medical School third and fourth year students. 3) Research opportunities available to graduate and undergraduate students through the Cancer Research Center in the following disciplines: immunology, biochemistry, microbiology, pathology, and biomedical engineering. 4) Development of the multidisciplinary atmosphere through admitting conferences, problems conferences, weekly teaching conferences, hematology/oncology conferences with the University of Missouri Medical School, oral pathology conferences, surgery seminars, surgical/pathology conferences, autopsy conferences and surgery grand rounds. 5) Presentations by Ellis Fischel State Cancer Hospital and Cancer Research Center health professionals to multidisciplinary conferences at health institutions and public educational facilities concerning the many aspects of cancer patient care; prevention, treatment, detection, diagnosis, nutrition, and other selected research topics. 6) Administration of professional programs on cancer management twice a year, with emphasis on the last program being "Prostate Cancer." The upcoming spring program is "Imaging As An Adjunct in Cancer Diagnosis." 7) Distribution of health care literature for patients, nonprofessional and professional health care workers, and segments of the public through the Cancer information Center and the Education Department. 8) Development of patient education audiovisual materials with emphasis on implant therapy, nutrition, tracheoesophageal puncture technique and drug reactions. 9) Administration of education/support programs for cancer patients and their families, emphasizing knowledge of the disease, communication skills, management of daily health problems, community resources and emotional well being.

Plans: In undergraduate and graduate education, the Ellis Fischel State Cancer Hospital and the Cancer Research Center will continue with current efforts in offering the Clinical Associate and Clinical Assistant the best exposure to

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cancer diagnosis, treatment and research. The development of a new area of the library especially suited to audiovisual materials for individuals or small groups will increase educational opportunities. In patient education, the expansion of the Cancer Information Center and addition of new audiovisual patient education materials will further our goal of offering accurate and helpful information to the cancer patient and his family. Semi-annual professional programs will continue to be a resource for health care professionals and students.

From 07/01/77 to 06/30/85

FY 81: \$109,729

Dr. J. Wendell Davis, St. Louis University School of Medicine,
1402 South Grand Boulevard, St. Louis, Missouri 63104

Objectives: This program is designed to provide an integrated understanding of the epidemiology, etiology, pathophysiology, treatment, and patient needs relating to neoplasia. The realization of these objectives is achieved through: (1) a second-year medical school course covering topics of oncologic relevance; (2) opportunities for medical students, at all levels of their training, to be involved in elective research projects dealing with oncology; (3) short courses for paramedical professionals and laypersons; (4) clinical associateships for post-intern study and training; and (5) ongoing colloquia on clinical aspects of cancer in which authorities provide lectures and visit with and discuss their area of expertise with faculty, students, residents and other interested persons.

Accomplishments: (1) Spring 1981 will mark the third year for the presentation of the second-year course, Integrated Oncology. The course has been well received by students in the trimester just prior to their entry into the clinical environment. (2) Each year, six to ten medical students have been afforded the opportunity to participate in clinical research experiences in diagnostic radiology, medical oncology, immunology, surgical oncology, pediatric oncology, molecular biology, radiation oncology, and other areas related to the study of neoplasia. Clinical associateships have been held by 17 individuals over the tenure of this program grant. These have provided post-residency training in diagnostic radiology, therapeutic radiology, genito-urinary oncology, gynecologic oncology, neurosurgical oncology, surgical oncology, and medical oncology. Ten colloquium speakers from as many different institutions have provided presentations and discussions of their research at approximately semi-monthly intervals throughout academic year 1980-01.

Plans: Of first order of priority will be the continuation of programs which are well started. The success of these indicates a realization of the importance of each on the part of curriculum planners and/or the consumers. Further outreach to medical and nursing personnel of the St. Louis community will be provided through continuing education courses in several areas related to understanding and treating cancer providing for the needs of the cancer patient. Continuing comprehensive efforts must be expended to completion of the Oncology Syllabus and the attendant tape-slide audiovisual presentations. During the coming academic year greater efforts will be made to infuse the Cancer Colloquia with speakers who have more nearly equal appeal to both clinicians and basic scientists. The series, ideally, should become a forum where scientists and clinicians of diverse interests can enter into dialogue. The result will be to provide a greater realization of the importance of discovery in the laboratory as it is ultimately applied to the cancer patient.

Program Director: Margaret H. Edwards, M.D.

From 07/01/76 to 06/30/85

FY 81: \$135,256

Dr. Melvin L. Reed, Wayne State University School of Medicine

3740 John R, Detroit, Michigan 48201

Objectives: The purpose and intent of the Clinical Cancer Education Program is to support and improve education for health professionals who are and/or will be responsible for dealing with the clinical aspects of cancer. The program has four major objectives: (1) continue support for multidisciplinary and elective aspects of oncological programs: (a) cancer "core" teaching, (b) student elective, (c) graduate, (d) postgraduate clinical cancer education program, and (e) continuing education in cancer related areas; (2) continue inventory, evaluation, and improvement of current cancer-related medical school curriculum as it pertains to both "core" curriculum and specialty and subspecialty programs; (3) utilize and prove the effectiveness of an interinstitutional oncology test item pool; (4) meet the identified and expanding need for oncology nurse specialists.

Accomplishments: A major review of current oncology education programs conducted by the Department of Oncology, which identified the faculty members responsible for each program, members participating in planning and execution, identification of existing and anticipated problems, alternative solutions, and priority and difficulty of each solution, was completed in December of 1980. Oncology faculty supported by the grant were utilized primarily to introduce clinical aspects of cancer to undergraduate medical students. A course on prevention and a two-hour outpatient experience for undergraduate students were also developed by faculty supported by the grant. Two new medical rotations designed to provide student exposure to oncology and to the oncologist as a role model were piloted in 1980-81. The grant also provided support for ongoing clinical clerkships and summer clinical assistantships, and also elective medical rotations in the oncology units of three community hospitals. Forty-eight one-month positions in oncology for medical interns, and forty-eight one-month positions for second and third year medical residents, were available in 1980-81. Four new clinical associates joined the postgraduate training program in 1980-81. A variety of continuing education programs such as the 13th Annual Cancer Symposium, were partially supported by the grant in 1980-81.

Plans: (1) a. Discuss and act on findings of the Departmental review; b. continue support for faculty providing cancer related education to undergraduate medical student; evaluate the two new medical rotations in oncology; c. & d. continue support for graduate and postgraduate medical education in oncology; e. continue support for continuing medical education in oncology. (2) Full assessment of the curriculum survey, including comparison with previous evaluations, identification of trends, and problems areas to be corrected. (3) Evaluate the instructor's perception of benefit, identify the number of items used from the item pool as opposed to the number of items originated by instructors, and assess whether or not increased testing for oncology objectives occurs compared to previous years. (4) Institute a two-year curriculum for training oncology clinical nurse specialists (projected September 1981).

Program Director: Margaret H. Edwards, M.D.

From 07/01/75 to 06/30/84 FY 81: \$68,052
Dr. Gordon W. Philpott, Washington University School of Medicine,
660 South Euclid Avenue, St. Louis, Missouri 63110

Objectives: The overall objective of the Washington University clinical cancer education program is to provide fundamental knowledge and skills for cancer management to a variety of undergraduate and graduate physicians, paramedical personnel, and members of the community. The program is directed toward all medical and paramedical professional personnel who may come in contact with cancer patients.

The specific objectives for the next four years include: (1) further revision of the sophomore oncology syllabus and increased emphasis on nutrition and epidemiology in this curriculum; (2) continued support of the summer student oncology program (clinical assistants in Division of Radiation Oncology); (3) improved interdepartmental coordination of the Clinical Associates' program (Pathology, Medicine, Pediatrics, Radiology) with clinical cancer fellows in other departments (Gynecology); (4) further development of combined outpatient cancer facilities with Medicine, Surgery and Radiation Oncology for "private" and resident patients at Barnes and Jewish Hospitals; (5) organization of at least one national cancer conference in St. Louis; (6) full accreditation of the Barnes Cancer Program by the American College of Surgeons; (7) organization of several multidisciplinary conferences, including a medical complex-wide tumor conference; (8) revision of the senior elective course.

Accomplishments: (1) Review and certification of the Cancer Program at the Jewish Hospital by the American College of Surgeons. (2) Reinstitution of the tumor registry at Barnes Hospital. (3) Revision of the sophomore oncology course and syllabus. (4) Plans for a medical complex-wide tumor conference run by the Clinical Associates in the Clinical Cancer Education Grant and the oncology fellow in Gynecology. (5) The successful planning and implementation of a number of the interdepartmental conferences dealing with cancer management held at regular intervals in the medical complex. (6) The planning and implementation of several large conferences designed primarily to disseminate newer information to the local physicians and in one case to medical students from several midwestern states (the American Cancer Society-sponsored Midwestern Regional Cancer Conference). (7) The continued success of the summer student program in cancer conducted by the Division of Radiation Oncology. (8) The successful implementation of the Clinical Associates' Program in Pathology with active participation of this associate in most phases of the Clinical Cancer Education program. Additional accomplishments such as the organization of a teaching slide file, have been achieved largely through the efforts of the Pathology associates. (9) Expansion of the computer-assisted instruction programs to Jewish Hospital. (10) Development of a number of computer programs in surgery and medicine to collect and analyze data on cancer patients in a similar fashion to Radiation Oncology. (11) The successful recruitment for and completion of the Clinical Associates' program in medical, pediatric, and radiation oncology. Five out of six of these associates are still in "academic medicine," contributing to cancer teaching in a significant way. (12) The successful institution and expansion of the programs in nutrition of surgical patients, in colorectal

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surgery, and in the Enterostomal Therapy School. (13) The completion of plans for combined outpatient cancer clinics at Barnes and Jewish Hospitals. (14) The recruitment of several valuable outside lecturers, notable Dr. Lauren Ackerman, Dr. Harvey Lerner and Dr. Ernst Wynder. (15) The institution of a new senior elective course in cancer organized and run by the Pathology Department, particularly the Clinical Associate. This course offers clinical material with emphasis on the multimodal nature of managing clinical patients. (16) Presentation of several conferences on cancer for community physicians, including the Seminars on Cancer run by the Radiation Oncology Division.

Plans: In the following three years we plan to achieve the objectives of the program using the important nucleus of the oncology faculty in several major departments, especially Pathology, Medicine, Surgery, Radiation Oncology and Pediatrics, under the guidance of the Cancer Education Committee. These individuals are active in the development, implementation and evaluation of the undergraduate, graduate and postgraduate teaching programs in oncology as well as the cCancer Committees of Barnes and Jewish Hospitals. Future plans will include assessment of the need and feasibility for formal training programs in nurse oncology and surgical oncology of Washington University.

From 07/01/75 to 06/30/84 FY 81: \$51,972
Dr. William R. Jewell, University of Kansas Medical Center,
39th and Rainbow Boulevard, Kansas City, Kansas 66103

Objectives: The improvement of multi-discipline cancer education in the biological and clinical sciences from students through house staff and oncology fellows to the practicing medical professional is the underlying objective of all activities of the grant. Specific objectives include: a closely defined cancer education program that transcends departmental teaching stressing an interdisciplinary approach to patient management; a dynamic and continuous program of evaluation to strengthen teaching; a coordinated program in medicine, nursing and allied health; a program for positive reinforcement and support by health care professionals for cancer patients and to engender an increasing interest in clinical cancer research.

Accomplishments: (1) In the beginning of this grant, the biggest need was to know exactly the cancer content of the medical school curriculum in order to evaluate the program. An Educational Psychologist has totally reviewed the teaching objectives of the cancer portions of the curriculum, compared these objectives with those of other medical schools, and evaluated the performance of graduates on cancer portions of the national boards. This provided the foundation for a continuing program of curriculum improvement in the medical school. (2) A year-long weekly schedule of an "Oncology Lecture Series" was presented which combined basic science with clinical aspects of the various types of cancer with basic science portions being presented by the faculty from the University of Kansas and Kansas State University as well as from the Medical Center. A clinical course rotating through Medical, Surgical, Pediatric and Radiation Oncology allows the medical student to observe the differing requirements of the disciplines concerned. (3) Oncology fellows have been supported by the grant which has assisted the clinical departments to develop approved fellowship programs so that now all clinical departments have accredited specialty programs and the clinical associates funded by the grant are rotated each year among the departments concerned. (4) An annual cancer symposium is conducted in which a specific site is given comprehensive coverage in a two-day program. The program is aimed at practicing professionals as part of the continuing education activity of the Medical Center. (5) The Continuing Education Division operates a circuit course for physicians and one for nurses which presents several programs, each in a different field, at eight different locations in Kansas. Once of the programs each year is devoted to cancer in which a team of specialists from KUMC/MACC makes the presentations. (6) Two regular publications; one receiving a wide distribution for physicians provides a bimonthly update on a cancer topic and abstracts of current cancer literature of interest to the primary care physician; the other is an in-house quarterly covering the activities of the many separate parts of MACC.

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(7) Medical students are encouraged to select a cancer field for their future activity by participation in a sponsored research project during the summer. The grant has supported 27 students in this activity in the last four years. (8) Oncology nursing is now receiving significant attention in the School of Nursing with special courses in both undergraduate and graduate programs. (9) The grants supports an Enterostomal Therapy program which admitted its first class in September, 1979 and 13 students completed the program in its first year. (10) A separate cancer library is established and growing, providing a resource for study convenient to the data source of the cancer registry. (11) A computerized regional cancer registry provides data on approximately 90,000 cases. The education committee of MACC has supported this activity by providing a part-time programmer to retrieve data for approximately 100 studies a year. (12) A new program being initiated in FY 81 is an effort to educate health professionals in the rehabilitation and support agencies available to cancer patients and how to make maximal use of these agencies in dealing with total care of the cancer patient. (13) A weekly tumor conference is conducted for selected medical students, house staff and cancer specialty trainees.

Plans: In addition to continuing the educational activities enumerated above, the Mid-American Cancer Center Education Committee will focus on developing an organized educational program to improve the physical care and emotional support of the cancer patient. A subcommittee is formed and specifically charged to develop this program. It is expected that Oncology Nursing will complete their plans for an oncology track in the graduate program in the School of Nursing. The new Dean of the School of Allied Health is interested in improving the cancer training of allied health personnel and will join the Cancer Education Committee. Particular attention will be paid to the effective domain aspects of the care of the cancer patient so that it will include allied health specialists.

Grant 17961: Electronic Laryngeal Prosthesis

From 05/01/75 to 04/30/81

FY 81: 0 (Ann. \$108,065)

Dr. Byron J. Bailey, Department of Otolaryngology, University of Texas Medical
Branch, Department of Otolaryngology, Galveston, Texas 77550

Objectives: The development of an acoustically "human sounding" voice substitute enabling a person who has undergone laryngectomy to speak while employing full use of the hands for other tasks.

Accomplishments: Project members have designed, built and tested in animals a satisfactory implantable electronic laryngeal prosthesis, along with the biomedical polymer encapsulate required by its materials and powering requirements. Three methods of percutaneous power and signal transmission have been investigated. Project members have developed a highly biocompatible elastoplastic covering for the prosthesis which meets the simultaneous demands of tissue compatibility, low moisture permeation, long implantation life, and great flexibility during implantation. Long-term studies of the acoustical output of these encapsulated sound generators in animals have ended at the end of the period of funding and the decision has been made to move to human volunteer trials. Much of the past six months has been spent in a search for a commercial source for manufacture of the device for human implantation. Project members have completed the developmental details regarding mechanical and electrical design and biological implantation. The permission of the local Institutional Review Board for human implantation has been obtained.

Plans: Project members have great interest in pursuing over the next several years the further steps leading to implantation of the prototype electronic laryngeal prosthesis in human volunteer subjects who have been unable to develop post-laryngectomy speech. Project members are unwilling, at this point, to pursue human implantation with custom made devices from our own electronics laboratory which lacks the capability for standardization and reliability that would be required for human implantation. Project members will pursue a manufacturing source possessing this capability, and when the appropriate devices have been obtained, the phase of human implantation will be entered.

Publications:

Devanathan, T. and Young, K.: Sound Intensity of bio-encapsulated electronic laryngeal prosthesis at room and body temperature. Journal of Biomaterials Research (IN PRESS)

Young, K. A., Bailey, B. J., and Devanathan, T.: Attenuation of sound due to bio-encapsulants in an electronic laryngeal prosthesis. Biomaterial, Medical Devices and Artificial Organs 8(3): 199-219, 1980.

Bailey, B. J., Young, K.A., and Everett, R. L.: Investigations in human implantable laryngeal prosthesis. Reprinted from American College of Surgeons 1980 Surgical Forum, Vol. XXXI, October 19-24, 1980, Atlanta, Georgia.

Young, K., and Devanathan, T.: Sound Output of electronic laryngeal prostheses at room and body temperature. Submitted to Biomaterials, Medical Devices and Artificial Organs, 1981.

Program Director: Lawrence D. Burke

From 07/01/75 to 06/30/83 FY 81: \$107,966
Dr. Donn J. Brascho, University of Alabama School of Medicine (Birmingham)
619 South 19th Street, Birmingham, Alabama 35233

Objectives: This program provides a continuing cancer education program for undergraduate medical students, housestaff, postgraduate physicians, paramedical personnel and patients. The key personnel supported by this grant participate in multidisciplinary clinical oncology teaching conferences, rounds and lectures for all levels of health professionals. Special emphasis has been given to development and acquisition of cancer educational materials. Medical student elective programs, summer clinical research programs and postdoctoral programs in oncologic subspecialty areas are supported. There has been development of new programs for physical therapists, occupational therapists, physician assistants, clergy and nursing personnel. There has been expansion of programs for postgraduate education through various clinical outreach programs. An important goal of the program is to strengthen the curriculum of medical students in cancer education.

Accomplishments: (1) Ongoing support of the weekly Oncology Conference, Gynecology Tumor Conference, Pediatric Oncology Conference, and the monthly Cancer Center seminars and Genitourinary Oncology Conference. (2) Support of the Radiation Oncology elective for junior and senior medical students (approximately 40 students per year), the Radiation Therapy one-month elective (approximately 3 students per year), the Gynecologic Oncology Clerkship for senior medical students and Radiation Biology Summer Research Program (approximately 3 students). (3) The grant has supported four clinical associates and three clinical assistants. The assistants have served as preceptors in the Department of Radiation Oncology. (4) There has been strong support of the nursing educational activities, including the Monthly Nursing Seminar, the Gynecology Nurse Practitioner Program, the Oncology Nurse Practitioner Training Program and the Post-Master Fellowship Program in Oncology Nursing Education. (5) In postgraduate activities, key personnel have acted as consultants in tumor conferences with presentations of didactic lectures or serving on tumor boards in at least 10 different hospitals throughout the state and region. They have supported a Colposcopy Satellite Clinical Program, a Melanoma Diagnosis and Treatment Project and a Medical Information Service by Telephone (MIST) Project. (6) Partial support has been given to at least three guest lecturers from outside the State annually. (7) Accomplishments in the area of patient education include the development of slide-tape programs on external radiation therapy and intracavitary radium therapy, and development of a patient education video-tape on bladder cancer. (8) A video-tape lending library has been established for use of physicians at the undergraduate and postgraduate levels throughout the State. (9) A concerted effort of evaluation of the multiple programs listed under the Grant has been underway for the last three years. Members of the faculty are actively involved in the ongoing Consortium Project with evaluation of cancer education sponsored by the American Association for Cancer Education and National Cancer Institute.

Plans: In the coming year continuing support of these ongoing programs and development and support of new programs are planned. Special effort is being made to expand the available teaching materials and to make them readily available to all physicians. A survey is now underway to compile and publish a

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list of all teaching materials and learning opportunities available in the Cancer Center. A major effort is being made to insure that cancer education be included to a greater extent in the undergraduate curriculum for medical students.

From 07/01/75 to 06/30/84 FY 81: \$148,058
Dr. Raymond E. Lenhard, Jr., The Johns Hopkins Oncology Center
600 North Wolfe Street, Baltimore, Maryland 21205

Objectives: The overall goals of this program are to prepare and administer a consistent educational program in cancer at Johns Hopkins through continuous curriculum input and monitoring. The program provides training opportunities in excess of the routine medical curriculum. A continuity of educational concept and philosophy in cancer has been established which encompasses many disciplines including the medical specialties, nursing, social service and other medical personnel. There is a particular emphasis upon integration of the basic and clinical sciences to medical care and clinical problem solving in cancer.

Accomplishments: (1) A mechanism for initiation of new educational programs in cancer and the evaluation of their acceptance has been established by the organization of a multidisciplinary Clinical Cancer Education Committee. (2) An organized educational approach has been accomplished with graded complexity of educational materials which spans the four years of medical school education. (3) Two new elective series in oncology have been developed and are presented on alternate years emphasizing basic and clinical cancer topics. (4) The Clinical Associates' program has been fully subscribed in internal medicine, gynecology, pediatrics and radiation therapy. In addition, programs with surgical pathology have been developed. This emphasis upon the education of physicians who have completed their residency training and who are specializing in cancer has strengthened the educational program as they participate in the teaching of medical students, nurses and other medical personnel. (5) Elective programs for medical students in basic and clinical cancer research have been provided by the multidisciplinary faculty of the Oncology Center. Publicity for the program and support of trainees has been carried out by the Cancer Education Committee. (6) Faculty and Clinical Associates in this program participate actively in nursing education at Johns Hopkins and also serve as a resource for the Outreach Program in the region. (7) The continuing education of physician assistants and radiation therapy technicians has been carried out by the faculty. A significant regional need for well trained personnel in cancer is being met by this educational project.

Plans: Plans for improving the educational offerings at the clinical level and in increasing the activities in epidemiology and biostatistics education are underway. Additional electives in clinical cancer and in cancer research are also being developed through the collaboration of The Comprehensive Cancer Center laboratory research programs. Continued input and monitoring of the cancer curriculum will be done by the Clinical Cancer Education Committee.

Program Director: Margaret H. Edwards, M.D.

From 07/01/78 to 06/30/84

FY 81: \$189,240

Dr. James F. Newsome, University of North Carolina School of Medicine
Chapel Hill, NC 27514

Objectives: To continue the development and planning of educational programs aimed at the ultimate achievement of optimal care of cancer patients in both the medical and dental schools; to enable students in the health professions to acquire basic knowledge of neoplastic disease including preventive, diagnostic, and therapeutic measures; to stimulate and expand efforts in cancer education and teaching to meet the changing needs of medical and dental education; to institutionalize the gains in cancer teaching programs with particular reference to increasing faculty strength, curriculum and interdisciplinary cooperation and expanded continuing educational programs for practitioners and paramedical persons.

Accomplishments: (1) Special educational programs and number of participants: Summer seminars in oncology for clinical assistants, 40; workshops in clinical oncology for nurses, 263; symposia for faculty, students, house staff and practicing physicians, 298; special seminars and lectureships, 435. (2) Clinical Assistant Program: Special educational and research opportunities have been provided in the following areas: immunology, 4; surgical oncology, 4; medical oncology/hematology, 9; pediatric hematology/oncology, 4; endocrinology, 1; neurosurgical oncology, 2; psychosocial aspects of oncology, 2; radiation oncology, 8; orthopaedic oncology, 1; gynecologic oncology, 1; dermatologic oncology, 1; and general dental oncology, 10. (3) Clinical Associate Program: Specialized educational and research opportunities have been offered at the post-graduate level for 19 associates in medical hematology/oncology, pathologic oncology, gastrointestinal oncology, medical genetics, urologic oncology, pediatric hematology/oncology, neurosurgical oncology, otolaryngologic oncology, and dentistry - oral medicine.

Plans: We propose to expand our educational opportunities with particular emphasis on the Clinical Assistant Program. Cancer nutrition, psychiatric oncology, and preventive oncology will receive major emphasis. Further interdivisional educational opportunities are proposed in neurooncology, leukemias, and lung cancer. A special exchange program in International Cancer Education is proposed.

Program Director: Margaret H. Edwards, M.D.

From 07/01/79 to 06/30/84 FY 81: \$115,572
Dr. Leonard A. Katz, SUNY/Buffalo School of Medicine
140 Farber Hall, Buffalo, New York 14214

Objectives: The program is designed to develop six educational programs for medical students, residents, attending physicians, and other medical personnel, and to increase interest in and knowledge of the problems of cancer. Further, it aims to affect the attitudes of the same medical community about the psycho-social aspects of cancer. The six programs include: (1) the Buffalo Cancer Syllabus, (2) monthly multidisciplinary cancer conferences, (3) a Cancer Selective, (4) a Cancer Elective, (5) a Clinical Associates' Program, (6) a Clinical Assistants' Program.

For the medical student, the project aims to integrate the components of education relating to cancer, and to present the general problems of cancer in a multidisciplinary manner. For the resident or practicing physician, the project aims to update knowledge of research in cancer and to integrate information on cancer from different disciplines.

Accomplishments: (1) Development of learning objectives and resource materials for the Buffalo Cancer Syllabus. The Syllabus integrates the components of undergraduate medical education which relate to cancer. (2) Continuance of monthly Multidisciplinary Cancer Conferences at five area hospitals. (3) Continuance of the Cancer Selective for a larger group of first-year medical students than served in 1979-80. In this seminar, students discuss general problems in cancer, including for example, environmental causes of a psychological adjustment to cancer. (4) Development of a one-week Cancer Elective for third-year medical students. (5) Support of five Clinical Associates (in pathology, radiology, pediatric oncology, medical oncology, and otolaryngology), whose duties are to teach medical students and residents, to develop materials for the Buffalo Cancer Syllabus, to participate in the Multidisciplinary Cancer Conferences, and to carry out research in oncology. (6) Support of twenty Clinical Assistants who participate in a variety of education experiences; assistance with development of the Cancer Syllabus or cancer research, and clinical experience in oncology.

Evaluations are made of each functioning program through questionnaires, and development of test items for evaluation of the effect of the Selective and the Syllabus on knowledge of cancer. Formative evaluations of the Multidisciplinary Cancer Conferences are made on a monthly basis; pre- and post- tests of attitudes about and knowledge of cancer are given to all students in the Selective and to a comparison group. In addition, presentations to both students and physicians of two guest lecturers: Dr. Richard Love (University of Wisconsin) and Dr. John Ultmann (University of Chicago). Dr. Love spoke on cancer prevention, Dr. Ultmann on the cure of Hodgkins Disease.

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Plans: Beginning in September 1981, the Cancer Elective will be offered to about twenty-third year medical students, and the Cancer Syllabus will be distributed to all 560 medical students. All other current programs will be continued, with any modifications suggested by the formative evaluations, and with new Clinical Associates and Clinical Assistants. Evaluations of program effects on increased knowledge and attitudinal changes will be carried out, and a longitudinal study of career impact will be begun.

From 07/01/78 to 06/30/84 FY 81: \$133,074
Dr. Emil Frei III, Sidney Farber Cancer Institute
44 Binney Street, Boston, Massachusetts 02115

Objectives: This program is designed to provide a unified, coordinated clinical cancer education program in gynecologic, medical, pediatric, radiation, and surgical oncology. The member institutions of this consortium include the Sidney Farber Cancer Institute and three other affiliated teaching facilities of the Harvard Medical School. Clinical cancer teaching is offered at the medical student, intern and resident, and clinical associate levels with emphasis given to a multidisciplinary integration of the component specialty disciplines. The program is conducted under the close supervision of senior staff, stresses patient care and clinical investigation, and offers an opportunity for interaction among clinical, psychosocial, and basic science divisions. Structured teaching programs for students, housestaff, and clinical associates are provided.

Accomplishments: The multi-institutional educational group which coordinates this Clinical Cancer Education grant has strengthened the quality and increased the visibility of clinical cancer education throughout the Harvard Medical area. Through an integration of faculty, an exchange of clinical associates, and an emphasis on clinical and laboratory investigation, this program which presently funds 17 clinical associates annually has helped establish an environment from which more than 80% of the "graduates" have chosen to remain in academic centers involved in research and teaching. Alumni of this program are now represented in the faculty of medical schools throughout the United States. In addition, the efforts of the faculty have resulted in a 30% annual increase in the number of medical students electing rotations in clinical cancer-related disciplines. Faculty involved in this program have additionally been instrumental in developing a bi-annual, five-day postgraduate course entitled Cancer Medicine which attracted "students" from 38 states and three foreign countries.

Plans: The goal of this clinical cancer education program is to create an atmosphere conducive for medical students, interns and residents, clinical associates, and practicing physicians to interact, exchange ideas, develop and execute innovative therapeutic programs, and to nurture the future leaders of academic oncology. Future activities will focus on further integrating the programs within our affiliated hospitals, attempting to enlarge the exposure of Harvard medical students to oncology, and to maintain the high value held for investigation which has set the tone for our program in the past.

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From 07/01/75 to 06/30/83

FY 81: \$112,013

Bernard Gardner, M.D., State University of New York-Downstate Medical Center, 450 Clarkson Ave., Brooklyn, New York 11203

Objectives: The program is designed to supplement the oncologic education of medical students beyond the regular curriculum. Students are specifically supported in extracurricular programs stressing clinical or basic cancer research. Special elective programs are designed to be given throughout the four years. Additional programs are given for housestaff, fellow and faculty education as well as outreach programs for community physicians. Multidisciplinary programs are stressed.

Accomplishments: (1) Electives for first and second year medical students involving cancer patient contact, seminars and prescribed reading programs under faculty supervision in a multidisciplinary setting (Breast Clinic) - 40 students average participation. (2) Seminars in Oncology - weekly series including six lectures in epidemiology for house staff, fellows and faculty. (3) Clinical Assistant Program (five students) in radiotherapy, research and epidemiology. (4) Clinical Associate Program - partially supported - Medicine, Radiotherapy, Pathology, not supported - Medicine, Pediatrics, Surgery. (5) Guest Lecturers in Medicine, Surgery at Grand Rounds for 80-100 housestaff, students and faculty. (6) Two-day program in Oncology for community physicians. Multidisciplinary program involving guest lecturers and attended by 150 physicians. (7) Poll of all faculty concerning teaching methods in Oncology, need for additional equipment and evaluation of syllabus. (8) Pretest of third year students to evaluate Oncology background and information base.

Plans: Future activities will continue and expand current interdisciplinary teaching programs. Additional guest lecturers are anticipated in conjunction with other ongoing programs in Oncology. A new fourth year elective is designed to reintroduce basic science material and its relevance to oncology for students. The preliminary design of the program has been worked out in a joint meeting of clinicians and basic scientists and will encompass one month with four mornings of lectures, a weekly seminar and afternoons spent in the cancer clinics. New assistantship programs in medicine and surgery will be implemented. A post-test of the third year class is planned to evaluate the cancer teaching program.

Program Director: Margaret H. Edwards, M.D.

From 07/01/75 to 06/30/84 FY 81: \$63,464
Dr. Noboru Oishi, John A. Burns School of Medicine and the Cancer Center of
Hawaii, 1236 Lauhala Street, Honolulu, Hawaii 96813

Objectives: The overall objective of the grant has been to develop a program designed to develop and use more effective educational methods for the medical and other health students, and post-MD associates, aimed at optimal cancer care with emphasis on trainees' acquisition of basic knowledge, clinical skills and appropriate attitudes. Departmental and interdepartmental programs improve and facilitate teaching and training of medical students and housestaff. A curriculum in interdisciplinary team care has emphasized the roles and working relationships of students from nursing, social work and medicine in health care. Teaching and training curricula are evaluated and needs for seminars and workshops are assessed by meetings of responsible faculty personnel. As a result, establishment of teaching and training has been realized through the development of an Interdisciplinary Oncology course, Clinical Associate Seminars, Hawaii Oncology Group meetings, Continuing Medical Education (CME) accredited workshops and seminars for practicing physicians and other health personnel.

Accomplishments: (1) Establishment of clinical assistantships for 31 post first- and second-year medical students in the area of basic and clinical oncology research. In general, research topics have included: geographic pathology, immunology, endocrinology, reproductive oncology, geriatric oncology and hyperthermia. (2) Development of an interdisciplinary health team approach to oncology care. A clinical assistantship program was developed for training of 31 medical, social work, nursing, clinical psychology, public health and nutrition students. This program is currently integrated into the regular elective programs and coordinated with the Schools of Medicine, Social Work and Nursing. In this current format, we have trained a total of 18 students from the three schools as well as one clinical associate. (3) With the establishment of the Clinical Oncology Associate Program, the Oncology Team Care was developed at Queen's Medical Center. In addition, Basic and Clinical Oncology seminars were established to enhance, through didactic lectures, the Clinical Associates' training program. These have included such topics as: biostatistics, pharmacology, hematopathology, and epidemiology. A total of three clinical associates have successfully completed this two-year training program. One of the Clinical Associates has passed the subspecialty Boards in Medical Oncology. (4) The Clinical Oncology Seminar Series has been developed and conducted mainly for practicing physicians. Conferences have included Prostatic and Testicular Cancers, Update in Ostomy Care, Phoresis Workshop, and Total Parenteral and Enteral Hyperalimentation. (5) Over the five-year period 22 visiting professors, lecturers, and consultants have been sponsored through this program. In addition the coordination of visiting professors sponsored by the American Cancer Society (ACS) has been successful. ACS Tutor Oncologists have participated in our program by conducting rounds and Cancer Center seminars. (6) Development of the Multidisciplinary Oncology Curriculum for third and fourth-year medical students. This curriculum includes didactics in the morning and related oncologic clinical cases in the afternoons. (7) The Hawaii Oncology Group Meetings has been established as a forum for physicians actively involved in treating

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oncology patients. These meetings are CME Category I accredited and are conducted once monthly. (8) The Annual Biomedical Symposium held at the John A. Burns School of Medicine encourages undergraduate and graduate students, medical students, residents, and postdoctoral fellows to present research papers. A special section in oncology has been established with an annual award to the best oncology related paper presented. (9) A total of 17 publications and 15 manuscripts have been presented and/or published as a result of support from this grant.

Plans: Future plans are to continue and improve current oncology programs, for medical students, housestaff, Clinical Oncology Associates, Interdisciplinary Oncology Team course, Biomedical Research Symposium (oncology section), visiting professors, postgraduate education for practicing physicians in the form of workshops and seminars, and the Hawaii Oncology Group Meetings. Designated faculty from the clinical departments of the School of Medicine will continue to be instrumental in the development and evaluation of all programs. In addition, new programs which will be instituted included the Multidisciplinary Oncology course and continuing oncology medical education for such health professionals as pharmacists. Oncology concepts will be integrated into a new geriatric elective for second-year medical students.

From 07/01/76 to 06/30/84 FY 81: \$63,048
Dr. Condict Moore, University of Louisville School of Medicine
Louisville, Kentucky 40232

Objectives: The ultimate purpose of this program is to sustain the best possible level of care of the cancer patient. This is done through (1) education programs both in-house (Oncology Lecture Series) and out in the state (Outreach Program) for students, (undergraduate and graduate), faculty, practitioners and nurses; (2) a Clinical Assistantship Program for medical students and a Clinical Associateship Program for residents and fellows; (3) an elective, "Concepts in Oncology", for medical students; (4) a Computer-Assisted Self-Evaluation Program (C.A.S.E.); (5) a nursing oncology program; and (6) various other cancer educational programs.

Accomplishments: (1) These include development of an Oncology Lecture Series of approximately ten in-house seminars a year which provides opportunities for practitioners of medicine and other health professionals to update their knowledge and experience in cancer through cancer talks out in the state; 21 talks were held during fiscal year 1979-80; (3) a Clinical Assistantship Program for 15 medical students each summer designed to give them experience in cancer outside of their regular curriculum; this is done through medical students working with clinical oncologists on our faculty to develop skills in the diagnoses, treatment and care of cancer patients; (4) a Clinical Associateship Program which provides a yearlong clinical cancer experience for four trainees giving them an opportunity to see and recognize cancer as a disease warranting multidisciplinary approaches; they learn numerous basic skills in the detection, diagnosis, treatment and rehabilitation of cancer patients, develop skills in research, including the design, conduct and analysis of clinical and basic cancer research studies; (5) development of a cancer elective "Concepts in Oncology" which provides students with an early opportunity to adopt a rational, scientific, and realistic view of cancer as a problem seeking solution; (6) a Computer-Assisted Self-Evaluation Program (C.A.S.E.) designed to provide students with a means to evaluate their own state of knowledge and skill in cancer; there are currently 12 cancer topics for students; and (7) the development of a nursing oncology program in cooperation with the School of Nursing devoted to the training and continuing education of nurses in cancer.

Plans: It is planned to continue the Oncology Lecture Series, the Outreach Program, the Clinical Assistantship Program, the Clinical Associateship Program and the Computer Assisted Self-Evaluation Program as Described above; our Nursing Oncology Program will be developed further in cooperation with our School of Nursing. A tracer study to evaluate the effectiveness of the core curriculum with regard to cancer education will be established.

Program Director: Margaret H. Edwards, M.D.

From 07/01/75 to 06/30/84 FY 81: \$14,918
Dr. James D. Cox, Medical College of Wisconsin
P.O. Box 26509, Milwaukee, Wisconsin 53226

Objectives: The program is committed to the expansion and improvement of clinical cancer education at the undergraduate and graduate levels through: (1) development of an Interdisciplinary Oncology Unit (IOU) as a point of focus for clinical cancer education; (2) coordination of the outpatient and inpatient activities of radiation, medical, surgical, and gynecological oncology; (3) increasing the amount of exposure of medical students and house staff to multidisciplinary care of cancer patients and the amount of didactic material related to cancer presented in the curriculum, and developing new means of evaluating the effectiveness of the teaching program in oncology. This program enhances the present and future quality of care of cancer patients throughout the region.

Accomplishments: Development of a dedicated inpatient unit, the Interdisciplinary Oncology Unit (IOU), with specialized nursing, pharmacy, and social work staff, as a resource for clinical cancer education. (2) Improved coordination of the core curriculum through the departments of pathology, pharmacology, microbiology, and the clinical sections. (3) Establishment of didactic sessions for students and residents, given by the senior staff in medical and radiation oncology. (4) Establishment of pathology (monthly) and radiology (weekly) conferences devoted to cancer. (5) Continuation of the highly successful program for students in the summer after the sophomore year; 17 students participated for 8 weeks in 1980. (6) Monitoring the impact of cancer education by yearly evaluation of MCW students' performance on the neoplasia questions in Part II of the National Board Examinations. (7) Creation of a new testing instrument using a video-tape to assess observation, hypothesis development, and clinical judgement in response to a simulated interview with a cancer patient. (8) Visiting consultants specifically invited to interact with two or more clinical or basic disciplines to enhance communication by formal and informal presentations. (9) Stimulating students to seek careers in oncologic specialties, especially radiation and medical oncology. (10) Introducing students to clinical investigations in cancer, and encouraging them to undertake small projects supervised by senior staff. (11) Establishment of a regional radiation therapy network which cares for 1500+ new cancer patients annually, and development of a high quality training program in radiation oncology.

Plans: The Medical College of Wisconsin will expand cancer education: a course will be established in the Biologic Effects and Applications of Ionizing Radiations, and more time in Pharmacology will be devoted to anti-cancer drugs. The IOU will be moved to a larger, recently renovated clinical unit, and an outpatient clinic will be developed as part of it for better continuity between inpatient and outpatient care. A handbook of cancer management for students and primary care physicians will be completed.

Program Director: Margaret H. Edwards, M.D.

From 07/01/75 to 06/30/84 FY 81: 112,085
Dr. William W. Shingleton, Duke Comprehensive Cancer Center
P.O. Box 3814, Durham, North Carolina 27710

Objectives: This program is designed to: (1) expand the teaching/learning experiences of medical, nursing and graduate students, resident physicians fellows and community physicians in the basic concepts of oncology and in the clinical management of cancer patients; (2) encourage interdisciplinary education in the field of oncology by developing better multidisciplinary cancer education experiences; (3) offer medical students and recent medical graduates study opportunities in specific problems of cancer by supporting their work in special oncology research projects.

Accomplishments: (1) Programs for medical students have been expanded to include an interdepartmental elective course for third year medical students which includes 32 two-hour didactic seminar sessions on basic and clinical aspects of human neoplasia; presently 18 medical and basic science graduate students are participating in the course. (2) The oncology clinical elective supplements oncology electives provided by each of the clinical departments and is designed for fourth year medical students, offering for the first time twice weekly seminars related to the clinical aspects of human neoplasia. (3) The program for clinical assistants offers indepth clinical and/or laboratory involvement in special projects relating to human cancer research; presently 12 clinical assistants are funded through this grant, and are working in clinical projects in internal medicine, pediatrics, surgery, obstetrics and gynecology, radiation therapy, cancer epidemiology and pathology. (4) The program for clinical associates includes clinical fellows in internal medicine, pediatrics, surgery, and obstetrics and gynecology. (5) Programs for senior and graduate nurses offer opportunities for independent study in oncology nursing in collaboration with oncology nurse clinicians in all of the clinical disciplines. (6) Programs for visiting professors have included 4 to 6 visiting professors annually who provide lectures, seminars and opportunities for interaction with learners throughout the Cancer Center. (7) Support of our clinical cancer education faculty, numbering 11 faculty members representing surgery, internal medicine, pediatrics, pathology, obstetrics and gynecology, radiation oncology, epidemiology, nursing, and education-evaluation permits the development, implementation and evaluation of all of the programs described above.

Plans: Our proposal focuses on supporting our cancer education faculty in its effort to evaluate more completely and improve the interdepartmental course in oncology and the oncology clinical elective, to provide a wider range of opportunities for clinical assistants and clinical associates, to integrate better the program for nursing students and graduate nurses into programs developing for medical students, and to improve evaluation tools for each of our programs in oncology education.

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From 07/01/75 to 06/30/84 FY 81: \$132,801
Dr. Richard G. Bakemeier, University of Rochester Cancer Center
601 Elmwood Avenue, Box 704, Rochester, New York 14642

Objectives: The program has the responsibility for coordinating and facilitating cancer educational activities at the University of Rochester and in the surrounding nine-county region for undergraduate medical and nursing students, residents in all clinical specialties, post-doctoral Clinical Associates, practicing physicians and nurses, and patients and their families. Specific activities include: (a) continual interaction with departments of the School of Medicine and Dentistry and with the School of Nursing, enabling cancer education to be incorporated into all years of the curricula; (b) definition of the objectives of each course relevant to cancer; (c) coordination of summer cancer fellowship program; (d) presentation of cancer programs at clinical staff conferences and at annual symposia for practitioners; and (e) periodic revision of the book "Clinical Oncology for Medical Students and Physicians".

The basic faculty and staff support provided by the Grant is expanded by a significant multiplier effect by drawing on the time and efforts of a much larger number of faculty and staff members who do not receive direct support from the Grant.

Accomplishments: These include (1) continual monitoring of the basic science and clinical medical curriculum and working with both the Medical Education (Curriculum) Committee of the School and with department members to expand cancer education activities in all four years of medical school; (2) establishment of a second year elective seminar series, "Introduction to Clinical Oncology", which is attended by about 25% of the class; (3) coordination of a series of "General Class Exercises" for the entire third- and fourth-year classes which provide multidisciplinary faculty groups to discuss current knowledge of the biology, epidemiology, diagnosis, and management of common malignancies; (4) coordination of conferences on cancer topics for residents in surgery, medicine, gynecology, and pediatrics; (5) coordination of a multidisciplinary post-doctoral education program for Clinical Associates; (6) invitation of visiting lecturers and coordination of publicity and other arrangements for their presentations; (7) coordination of clinical departmental and interdepartmental cancer electives for fourth-year medical students; (8) coordination of an extracurricular summer cancer fellowship (Clinical Assistantship) program for 35 to 40 medical and nursing students annually; clinical assistantships are arranged in basic research laboratories, and in clinical experiences in oncology; experiences have been provided in preventive oncology, epidemiology, and psychosocial aspects of oncology; (9) periodic revision of the cancer syllabus "Clinical Oncology for Medical Students and Physicians"; this multidisciplinary cancer text was first prepared by the Rochester faculty in 1967 as a direct result of inter-departmental coordination through the Cancer Education Committee of the Clinical Cancer Training Grant Program; distribution has been through the American Cancer Society to most of the medical students in the United States and to many practicing physicians, nurses and oncologic faculty members; (10) preparation of a "Handbook of Basic Science Cancer Education Objectives"; (11) evaluation of all cancer education activities; and (12) planning and

Program Director: Margaret H. Edwards, M.D.

coordination of an annual symposium on cancer topics for practicing physicians and nurses.

Plans: These include (1) integration of a second-year elective "Introduction to Clinical Oncology" into the second-year curriculum for all students; (2) revision of the syllabus "Clinical Oncology for Medical Students and Physicians"; (3) creation of more attractive Multidisciplinary Oncology Electives for fourth-year medical students; these electives will seek to increase student contact with cancer outpatients, and will also emphasize psychosocial and epidemiologic aspects of clinical oncology; (4) emphasis in the post-doctoral Clinical Associate program on the development of research- and teaching-oriented academic oncologists; and (5) expansion of cancer education activities for regional practicing physicians and nurses.

From 07/01/76 to 06/30/84 FY 81: \$62,733
Dr. Michael A. Friedman, University of California
San Francisco, California 94143

Objectives: This education program is designed to offer the largest possible exposure of cancer related materials to the widest possible audience. Included in this audience are undergraduate, graduate, and postgraduate physicians, nurses, pharmacists, dentists, as well as the lay community. Special attention is focused on the undergraduate medical student, as well as the postgraduate clinical associate in both Medical Oncology and Radiation Oncology. The overall theme of this program is that a successful education effort allows the trainees to be effective teachers. That is, those people who understand the discipline and who are taught how to teach will understand the subject better than someone who passively receives information. We believe that in order to make effective teachers the trainees must learn effective teaching techniques, know their subject matter in depth, be discriminating in terms of the quality of the work, and passionately care about the subject matter.

This activity is the joint effort of a number of different departments within the University of California, San Francisco, with broad participation by the Departments of Medicine, Radiation Oncology, Surgery, and Pathology.

Accomplishments: In objective terms, the accomplishments may be summarized as:

(1) The training of two Medical Oncology clinical associates each year (with demonstrated abilities as judged by Board certification). These clinical associates have participated not only in educational activities (instructing them in how to care for the patient and family with cancer) but the training also has allowed them to be productive clinical and laboratory scientists, rounding out the fullest extent of their education. (2) The speciality Clinical Pharmacy Training Program in Graduate Oncologic. These individuals have had special exposure to the treatment of patients with neoplastic disease and they have carried out their own research programs looking at drug pharmacology, extravasation models, and clinically useful drug interactions. (3) Oncologic Nursing courses are given on the undergraduate and graduate levels by the faculty, not just at this campus, but addressing a wide range of nurses throughout the Northern California area. (4) Extended interdisciplinary conference activities discuss both patient care and general matters, especially focusing on the areas of head-and-neck cancer, melanoma, gynecologic malignancy, breast cancer, and lymphomas. (5) Increased enthusiasm and participation occurs in scheduled cancer courses for the undergraduate medical, nursing and pharmacy student level. (6) Subjectively there is greater appreciation and sensitivity to the physiologic, biochemical and physiologic, biochemical and psychologic aspects of cancer care by all the appropriate disciplines.

Program Director: Margaret H. Edwards, M.D.

Plans: The plans for the projected next several years for this education effort include more intensive application of some of the programs which we have currently demonstrated to be so effective on this campus. New courses will be devised for the medical students and nursing students and subspeciality in-depth participation by the Graduate Schools of Nursing and Pharmacy are planned. Continued activities by the Medical Oncology and Radiation Oncology clinical associates should yield the training of more high-grade academic teachers than in the past.

From 06/01/78 to 05/31/84

FY 81: \$84,133

Dr. Jack Geller, Medical Education Department, Mercy Hospital and Medical Center, San Diego, California 92103

Objectives: The major objective of this project is to compare histologic grading of prostate cancer to biochemical markers of androgen mediated action for accuracy in predicting the incidence and duration of clinical response of metastatic prostate cancer to endocrine or ablative therapy. The key biochemical marker chosen for study is tissue DHT concentration. Other markers to be measured in prostate tissue include prostatic acid phosphatase, G6PD, alkaline phosphatase and both nuclear and cytosol androgen receptors. Correlation of all parameters with clinical response to therapy will be examined by both individual and multi-variate analysis to determine the best predictor of response to hormonal therapy.

Accomplishments: Forty-two patients, 29 with Stage D2 cancer and 13 with Stage D1 or C cancer have been entered into our study and treated. Five Stage D2 patients have had objective progression of their disease. Twenty-two additional Stage D2 patients have had initial remissions lasting greater than six months following initiation of anti-androgen therapy. Fourteen of these 22 patients currently in remission for from six to 48 months are being followed while the remaining patients have either relapsed or died of unrelated causes.

DHT levels were less than 2.0 ng/gm in four out of five patients with objective progression of disease while DHT was greater than 2.0 ng/gm in 21 out of 22 patients with initial remission of greater than six months following therapy. In the same patients, histological Grade 2 1/2-3, suggesting a poorly differentiated tumor was noted in all five patients with objective progression. However, in 22 patients with initial remission greater than six months, 12 had well differentiated tumors (Grade 1-2) while ten were poorly differentiated (Grade 2 1/2-3). These data strongly suggest that DHT levels are better predictors for occurrence of initial remission in patients with metastatic prostate cancer than histologic grading.

Stage D or D patients--13 patients have been entered into this study without symptoms except for prostatism and are currently being followed.

The funding has been from the National Institutes of Health through the Roswell Park National Prostate Cancer Study Group. Total patient tissues studied and patients followed to date is 42. Lectures given on this topic during the year include the Atlanta Regional Cancer Seminar in November of 1980 and a talk to be given at the Endocrine Society in June of 1981.

Plans: We plan to continue to follow all patients entered into this study to determine the disease-free interval and survival in order to correlate these parameters with tissue DHT and other biochemical markers of androgen action. This work will allow conclusions regarding the usefulness of DHT and other biochemical parameters as predictive markers for clinical response to therapy in prostate cancer.

Program Director: Andrew Chiarodo, Ph.D.

Publications:

Geller, J. and Albert, J.: The Effect of Aging on the Prostate. In Endocrine Aspects of Aging, Korenman, S. G., (Ed.) Elsevier North-Holland, New York, 1981.

Albert, J. and Geller, J.: The type of Current Frequency Used in Transurethral Resection of Prostate Affects the Androgen Receptor. IRCS Med. Sci 8:113, 1980.

Geller, J. and Albert, J.: Effects of Heat and p^H on Radioimmunoassay and Activity of Prostatic Acid Phosphatase Compared. Clinical Chemistry 26:(7) 1110-1111, 1980.

Geller, J., Albert, J., Yen, S.S.C., Geller, S. and Loza, D.: Medical Castration of Males with Megestrol Acetate and Small Doses of Diethylstilbestrol. J. Clin. Endocrinol. Metab. 52:3, 576-580, 1981.

Geller, J., Albert, J., Loza, D., Geller, S., Stoeltzing, W., and de la Vega, D.J.: DHT Concentrations in Human Prostate Cancer Tissue. In Steroid Receptors and Hormone-Dependent Neoplasia from 1st Innsbruck Winter Conference on Biochemistry in Clinical Medicine, 1978, Austria. Masson Publishing U.S.A., Inc., Chapter 15, pp. 113-138, 1980.

Geller, J., Biochemical Study of Prostate Cancer Differentiation. In Prostatic Cancer Newsletter, National Prostatic Cancer Project 8 (1) Winter 1980.

Geller, J., Albert, J., Nachtsheim, D., Loza, D. and Geller, S.: Correlation of Cancer Tissue DHT Levels with Clinical Remission in Advanced Prostate Cancer. The Endocrinology Society Program - Poster Presentation Cincinnati - June 1981.

From 07/01/75 to 06/30/84

FY 81: \$58,427

Dr. Norbert J. Burzynski, University of Louisville, School of
Dentistry, Louisville, Kentucky 40232

Objectives: The purpose of this Clinical Cancer Education Program is to instruct and update undergraduate and graduate dental students, practicing dentists and parodontal personnel on the concepts of prevention, detection, diagnosis, treatment and rehabilitation of oral-facial cancer. Emphasis is placed on the Health Sciences multidisciplinary approach to the multifaceted aspects of cancer. Specific aims include experiences as Clinical Cancer Educational Assistantships; coordinating efforts of the core and peripheral curriculum; providing continuing cancer educational opportunities to faculty, practitioners, auxiliaries and enrolled students; developing innovative educational programs in clinical cancer; improving evaluation techniques and emphasizing the multidisciplinary approach in cancer knowledge.

Accomplishments: The program has: (1) emphasized cancer content within the core curriculum, wherein students have become attuned to the problems of cancer biologically, psychologically, and productively; (2) encouraged the development of elective and selective courses for upper classes; (3) made students aware of the function of a Tumor Board and Tumor Registry; (4) allowed students with special interests and concerns to participate in the delivery of care and ramifications of therapy (surgery, medical oncology, therapeutic radiology); (5) enabled the oral-dental and maxillofacial programs to become integral programs in the Regional Cancer Center; (6) stimulated the interest of auxiliaries in cancer detection, treatment and rehabilitation; (7) become the initial stimulus for an outreach program to component medical and dental societies and hospitals in greater Louisville and Western Kentucky; this program is coordinated by the Regional Cancer Center; (8) allowed for the annual continuing education presentation in **oral cancer for practitioners** and auxiliaries; (9) allowed for the development of an annual multidisciplinary symposium on oropharyngeal cancer; (10) been the stimulus in developing a Cancer Center Speakers Program, wherein authorities in various disciplines are invited to the Cancer Center to share their knowledge with the faculty, students and staff; (11) given the opportunity to numerous students to participate directly in cancer education, by receiving a Clinical Cancer Educational Assistantship; this program has been most beneficial to those students who wish to further their knowledge on cancer beyond the core curriculum content; (12) allowed development of a computer assisted self evaluation program, which has various Health Sciences consortium participating; (13) been a stimulus in developing and maintaining a Cancer Center Newsletter for professionals, auxiliaries and segments of the public.

Plans: Emphasis will be on the dissemination of knowledge relative to cancer control, extension of the Clinical Cancer Assistantship program to qualified applicants, maintenance and upgrading of outreach and continuing education programs, review and modification of evaluation, and development of an educational control program on oral-facial cancer in the new Louisville Regional Cancer Center.

Program Director: Margaret H. Edwards, M.D.

From 07/01/76 to 06/30/82 FY 81: \$85,566

Dr. Edward T. Kremenz, Tulane University School of Medicine
1430 Tulane Avenue, New Orleans, Louisiana 70112

Objectives: This program is designed to expand and enrich clinical cancer education at Tulane Medical School for medical students, postgraduate trainees, practicing physicians and paramedical personnel. This will be done by improving interdisciplinary teaching through Tumor Conferences, seminars and a new second-year "Cancer Clinics" course. Consultants in education will be invited to critique and evaluate the program. Guest lecturers will be provided for students and graduate medical personnel. Library AV facilities are to be expanded. Four clinical associates in Medical and Surgical Oncology will be appointed and 16 student clinical assistants will be appointed each summer. New and revised programmed texts on cancer are being prepared by medical students under the supervision of Dr. Robert Ryan. Additional teaching materials are to be acquired and distributed. Key teaching personnel are supported in part to aid the program.

Accomplishments: Core cancer curriculum includes the new "Cancer Clinics for sophomores consisting of interdisciplinary seminars on 12 different tumor sites with emphasis on good prognosis patients. This course is designed to improve attitudes of the novice physician toward cancer patients and an evaluation of the student attitudinal profile is underway. Junior and senior students receive experience in the various medical and surgical oncologic disciplines as clinical clerks working on wards and clinics with a wide variety of cancer patients. This experience is enhanced by Interdisciplinary Tumor Conferences, scheduled oncology lectures, seminars, guest lecturers, and visiting professors. Elective courses are also offered and include the Biology and Chemistry of Steroids as related to cancer therapy, Therapeutic Radiology, Otorhinolaryngology, Gynecology and Pediatric Oncology. The Oncology AV materials in the general Medical Library have been upgraded and expanded. Each student receives a copy of Clinical Oncology for Medical Students and Physicians, and Charity Hospital Tumor Registry Monograph, the Breast Cancer Digest of NIH, the ACS Professional Education Oncology Publications, five oncology programmed texts, and the six issues of Ca published each year. Four clinical associates in Medicine and Surgery are currently appointed and the clinical associates for next year have been selected. There were 8 clinical assistants last summer funded by NCI. Seven were oncology clinical clerks, while one participated in oncologic laboratory research. Four additional clinical assistants were funded by the ACS and participated in the program.

The Cancer Education Program was evaluated by Dr. Richard Bakemeier, who came by our invitation to review, critique and evaluate the program.

Plans: Continued refinements will be made in the series of "Cancer Clinics" lectures as various faculty gain experience with the program. The use of supplemental teaching facilities such as slides, the Library AV collection, Charity Hospital Tumor Registry materials and programmed texts will be expanded. Stimulating visiting faculty are being sought while current clinical associate and clinical assistant programs will be strengthened. Core curriculum will be under continuing review and improvements will be made by education consultants and key grant administrative personnel.

Program Director: Margaret H. Edwards, M.D.

Grant 18009: Clinical Cancer Education Program

From 07/01/76 to 06/30/82 FY 81: \$133,133
Dr. Robert Bases, Albert Einstein College of Medicine,
1300 Morris Park Avenue, Bronx, New York 10461

Objectives: Our efforts focus on teaching undergraduate medical students the management of cancer largely as an outpatient and multidisciplinary enterprise. Long-term follow-up of a few selected patients by first-year medical students was chosen to give them greater insight into the psychological and socio-economic consequences of the disease and its management than had been possible previously.

We hope to improve the knowledge and training of medical students who will not specialize in oncology.

Accomplishments: Selective in "Life Study of Cancer Patients". Thirty first-year students in groups of ten with one faculty Oncologist Preceptor for each group meet weekly. Each student is assigned to one or two patients who are followed continuously through the course of the first year. Students later review their patients' management with Pathologists, Radiologists, Medical Oncologists, and other specialists. They attend clinics with their patients, perform simple diagnostic procedures and attend conferences concerning their patients. Later on, they review their own patients' X-ray films and pathology slides and other relevant data with appropriate specialists. We have been authorized to accept up to forty students in this program.

We have been authorized to give a series of six one-hour lectures in oncology to cover topics that may be missed in the curriculum in the second year. The evaluation of this program (by the evaluators) indicates that it is understood, it is achieving its goals, and is well accepted and popular with the students.

The third year teaching includes bedside rounds. These are informal one-hour rounds at the bedside involving specialists i.e., a multidisciplinary teach which includes Medical Oncologists, Radiotherapists, Surgeons, Pathologists, Diagnostic Radiologists and others. One case is discussed and six to ten third-year students participate.

Plans: Our program will continue with special emphasis on the first year "Life Study of Cancer Patients" Program, The Clinical Assistants Program, and the lecture series in the second year and the Return to Science, to be expanded because of its popularity. Greater emphasis will be allowing students to participate in screening and early detection clinics.

Program Director: Margaret H. Edwards, M.D.

From 07/01/79 to 06/30/84 FY 81: \$128,239
Dr. John W. Athens, University of Utah College of Medicine
Salt Lake City, Utah 84132

Objectives: The objective of the Clinical Cancer Education program is to improve the cancer education at all levels in the regional medical community. This will provide for more and better trained health care personnel which should result in improved cancer patient management.

The Clinical Cancer Education programs impacted by this grant are extensive including the following: ongoing curriculum review and development for medical students; practical education experiences for interns and residents; direct support of clincial associates in medical, radiation and gynecologic oncology; support for an outreach program for physicians and nurses in the large geographic area through tumor board conferences and lectures; support for nursing instruction in special oncologic nursing courses; and staff time to support education for pharmacy students, nutrition students and other allied medical personnel.

Accomplishments: Medical Students - The curriculum of the organ system courses has been reviewed with attempts to increase the content of cancer education in each organ system. National Board scores were reviewed to identify areas of weakness. Improved objectives for the students have been developed. Many students now participate in oncology electives. Two medical students have been sponsored during summer research projects. Their projects evaluated testing of mutagenicity of polycyclic ethers and investigating pyrolysis mass spectrometry in acute leukemia.

Interns and Residents - A series of formal lectures is given to the housestaff during the year. Each patient with cancer is discussed in detail with them. Attendance by housestaff at tumor boards has increased. The last group of medical residents taking internal medicine board exams scored in the 99th percentile in oncology indicating the success of the program. Also, a high percent of the housestaff who go into subspecialty areas have entered oncology.

Clinical Associates - Nine medical oncology-hematology, one radiation and one gynecological oncology clinical associates are in the training program. Five are directly supported by the Cancer Education grant. They all receive instruction in patient care, clinical research through SWOG and GOG, and some elect further training in laboratory research.

Postgraduate Physicians - Through cancer conferences sponsored through this grant and by the University, over 80 outreach programs have been given in community hospitals attended by over 1,200 physicians. Additional teaching conferences given at the University have been attended by 900 physicians. Regular consultations with referral letters provide instruction for private physicians as well.

Nursing Education - Regular courses have been developed in the nursing curriculum in addition to multiple outreach conferences reaching over 800 nurses in the past year.

Program Director: Margaret H. Edwards, M.D.

Allied Health Personnel - Lectures to pharmacy students on breast cancer, colon cancer, lymphomas and cancer chemotherapy; nutrition students working in oncology clinics, ward rounds and education conferences; lectures to social workers and rounds with them.

Cancer Education Consultants - Three visiting speakers have been sponsored by the Cancer Education grant to provide "outside expertise" at conferences attended by 295 physicians and students.

Plans: To continue the significant impact the Clinical Cancer Education grant has on the cancer problem in this area, the following goals have been set for the next year: (1) Maintain the current extensive Cancer Education Program with continued evaluation to determine areas of weakness. (2) Continue the clinical associate program for five trainees--three Medical Oncology, one each in Gynecologic Oncology and Radiation Oncology. (3) Recruit a surgical oncologist and begin development of a Surgical Oncology clinical associate program. (4) Strengthen the Pediatric Oncology training program. (5) Increase the number of Visiting Cancer Teaching conferences to include two additional hospitals.

From 05/01/75 to 09/30/84

FY 81: \$67,141

Dr. David M. Lubaroff, Department of Urology, University of Iowa, Iowa City, Iowa 52242

Objectives: This study is designed to investigate whether immunologic mechanisms play a role in observed remissions of metastatic cancer of the prostate following cyrosurgical treatment of the primary tumor. Experiments utilize the Dunning R3327 adenocarcinoma of the Copenhagen rat as an animal model of the human disease. We wish to determine whether cryosurgery can induce antibody and/or cell-mediated immunologic responses to tumor antigens. If cryosurgery does induce immunologic responses, we shall examine their role in the regression of metastatic lesions. Experiments will include the use of various immunopotentiating agents along with cryosurgery in an attempt to produce the strongest responses possible against the prostatic tumor antigens. Should we determine that immunologic mechanisms are responsible for metastatic tumor destruction, we plan to study the mechanism(s) involved.

Accomplishment: In the past we have successfully characterized the Dunning R3327 tumor as an adequate model of human prostatic cancer, demonstrated the ability to destroy the tumor by cryosurgery and to induce xenogeneic, allogeneic and syngeneic anti-tumor immunity. Our current and immediate future research plans continue towards our goal of determining the role of cryosurgically-induced immune responses on primary and metastatic cancer of the prostate. Experiments in progress or planned include (1) induction of antitumor immunity by cryosurgery with and without the adjuvant effect of immunopotentiating agents (BCG, *C. parvum*, levamisole, etc.), (2) establishment of highly metastatic tumor lines for studies of immune effects on disseminated tumor, (3) quantitate the localization of radiolabeled tumor cells, (4) examination of the heterogeneity of prostatic cancer using *in vivo* variants of the Dunning tumor and *in vitro* cell lines established from the original R3327 rat lesion, (5) investigation of what role natural killer (NK) cells play in anti-tumor immunity in this prostatic cancer system, and (6) experiments on the mechanism(s) of anti-tumor immunity by studying the role of different lymphocyte populations in the destruction of prostatic cancer.

Plans: Much of our future plans hinge on results obtained in our current experiments. All our investigations again are aimed at demonstrating a role for cryosurgically-induced immunity on primary and metastatic cancer of the prostate. In addition to looking for a role of antibody and lymphocytes in destruction of tumor, we shall examine what role, if any, these effector molecules and cells play in suppression of an anti-tumor response.

Publications:

Article published in a periodical:

Lubaroff, D.M., Reynolds, C.W., Canfield, L., McElligott, D. and Feldbush, T.L.: Immunologic Aspects of the Prostate. *The Prostate*, (In press), 1981.

Greiner, D.L., Reynolds, C.W. and Lubaroff, D.M.: Functional T Cell Subpopulations in the Rat. *J. Immunol.*, (In press), 1981.

Program Director: Andrew Chiarodo, Ph.D.

Article in a book:

Lubaroff, D.M., Reynolds, C.W., and Canfield, L.: Immunological Aspects of Experimentally Induced Prostatic Cancer. In: Ablin, R. (Ed): Prostatic Cancer New York, Marcel Dekker, Inc., 1981, (In press).

Lubaroff, D.M. and Feldbush, T.L.: Immunotherapy of Prostatic Cancer. In: Loening, S.A. and Culp, D.A. (eds). Genitourinary Oncology. Philadelphia. Lea and Febiger. 1981. (In press).

From 09/30/70 to 06/30/83 FY 81: \$62,801
Dr. James Cerilli, Ohio State University,
410 W. 10th Avenue, Columbus, Ohio 43210

Objectives: The overall objectives of the Cancer Education Program are to: (1) strengthen the oncology training programs in the Departments of Medicine, Pathology, Pediatrics, Radiation Therapy, Surgery and Obstetrics and Gynecology; (2) initiate a broad program of elective courses for our residents and medical students to be given under the direction of our Clinical Associates and supervising faculty; (3) improve the documented deficit in many of the areas of Southeast Ohio in the area of cancer by strengthening our patient services and educational programs in this area. The ultimate goal to be realized from this program is an increase in the supply of physicians with extensive training in cancer, thereby an improvement in the care available to the patient with cancer.

Accomplishments: (1) Provides training and support to six clinical associates; two in the department of Hematology/Oncology, two in the department of Surgery, one in Pathology and one in Pediatric Oncology. Their training activities include clinical care of inpatient cancer patients, out-patient cancer clinics, tumor boards, seminars, conferences, treatment planning sessions, cancer research and teaching. (2) Continuing input into the educational efforts of the Ohio State University Comprehensive Cancer Center, including patient and public education and learning opportunities provided to medical and post-graduate students. (3) Provides support to visiting professorship program in cancer, providing presentations on "Molecular Mechanism of Cyclic AMP in Growth Regulation of Breast Cancer", "The Role of Surgery in Diseases of the Thyroid Gland", and "Anti-Tumor Activity and Metabolism of N-methyl Containing Drugs". (4) Training and support of Clinical Assistants in the areas of Obstetrics-Gynecology and Radiation Therapy whose training activities include attendance and participation in Surgery and Gynecology tumor boards, departmental conferences, Gynecology clinic, in-patient rounds and cancer research activities. (5) Provide curriculum input in under-graduate elective course in cancer (detection and prevention) which has a current enrollment of 500. (6) Regularly scheduled cancer related programs on the Ohio Medical Education Network (OMEN) which serves over 2,000 physicians at 150 hospitals.

Plans: To meet the need of physicians trained in cancer, activities in 1981-82 will include continued support of the Clinical Associate and Assistant programs in the areas of Hematology, Pathology, Pediatrics, Surgery, Obstetrics and Gynecology, and Radiation Therapy. Additionally, elective courses in cancer for undergraduate and medical students will be continued and further programs in cancer are scheduled for the 1981-82 OMEN season to meet the continuing education needs of practicing physicians in Ohio and neighboring states. Evaluation of these programs is done on an on-going basis and modifications made in any area as necessary.

Program Director: Margaret H. Edwards, M.D.

From 07/01/76 to 06/30/84 FY 81: \$118,650

Dr. Richard Caplan, University of Iowa College of Medicine
Iowa City, Iowa 52242

Objectives: This grant supports a wide variety of educational activities aimed at medical students, house officers and fellows, practicing physicians, and also other health professionals. Our purposes are correspondingly diverse and relate to the type and level of intended learner, but in general are aimed at increasing the knowledge, skills and attitudes that will foster prevention for those at risk, and early diagnosis and optimal management for patients with cancer, especially drawing attention to psychosocial and rehabilitative needs. We're striving to inform and motivate our various learners to want to know about cancer and deal with it effectively.

Accomplishments: (1) This year we have worked toward identifying the many instructional activities about cancer that occur throughout our undergraduate medical curriculum. (2) Five of our clinical associates have completed their formal training. (3) Twenty-three medical student seniors have elected one-month experiences as clinical assistants. (4) Our Cancer Seminar Series of distinguished visitors has almost doubled the number of its attendees over previous years. (5) Two instructional videotapes were developed to orient women about to have radiation treatment for cervical carcinoma. (6) A seminar series on bio-medical ethics was given support. (7) Instruction was given to pediatricians in community-based care for children with malignant disease. (8) Several kinds of continuing education were provided to practicing physicians, nurses, and dentists, including special instruction in head-and-neck tumors. (9) An interdisciplinary instructional unit was expanded and provided to medical sophomores and physician assistant students during the "Introduction to Clinical Medicine" course. (10) Written information was arranged to be sent to a network of practicing surgeons and radiation therapists, and another series of cancer articles was provided in the medical student monthly newspaper. (11) Support was given to a graduate student in activities therapy who, in turn, supervises student interns working with a population of children with malignant disease. (12) Several smaller projects were undertaken to stimulate faculty innovation and student interest in cancer projects, including assistance to continuing oncology education for an audience of nurses and another of dentists. A major, and perhaps most important long-range development was the formation, through the initiating and organizing thrust of our cancer program and its educational effort, of an interdisciplinary cancer center at our institution.

Plans: In the coming year we expect to continue support for a total of 26 projects (many enumerated above) that aim toward the fulfillment of our general and specific objectives. Evaluation continues to be a weak spot and we mean to increase our effort toward more satisfying and meaningful assessment of these many special projects in cancer education.

Program Director: Margaret H. Edwards, M.D.

Grant 18019: Clinical Cancer Education Program

From 07/01/76 to 06/30/85 FY 81: \$159,451
Dr. Peter J. Mozden, Boston University School of Medicine
80 East Concord Street, Boston, Massachusetts 02118

Objectives: The objectives of this program are to develop and to demonstrate an approach to cancer education that will be recognized by the institution and the region as resulting in optimal care and management for cancer patients and effective educational experiences for multiple levels of professional staff, well beyond what might be expected in an average medical school setting. The program is aimed at medical students, house staff, graduate and community physicians, nurses, social workers and hospital administration. The teaching methodology intends to demonstrate a multi-disciplinary approach. The fundamental need to correlate basic and clinical sciences in the care of cancer patients, and to provide opportunities for community physicians to participate in clinical research advances is stressed.

The program provides the planning and coordination of a wide variety of educational methodologies to reach the program objectives.

Accomplishments: (1) Development of an annual 30-hour curriculum in cancer for medical students. Development of an annually updated syllabus of instruction. Participation of 24 multidisciplinary faculty, representing 12 separate departments. (2) Development of a new seminar course on the Epidemiology of Cancer, given monthly. (3) Development of 19 cancer electives of 1-3 months' duration for medical students in several basic sciences, clinical research and clinical experiences. (4) Development of a structured 2-year program of education for post-graduate physicians in medical, surgical and radiotherapeutic oncology. Six clinical associates are currently in the program, 2 each in medicine, surgery and radiation therapy. (5) The establishment of categorical sections on oncology in medicine, surgery and in radiation therapy, each with its own full-time oncologic faculty to pursue organized and coordinated objectives in cancer education and patient care. (6) The establishment of categorical clinical cancer units in both Medicine (36 beds) and in Surgical Oncology (30 beds) to pursue the educational and clinical research objectives of this program. (7) Development of a summer program of cancer educational projects for 8 clinical assistants (medical students) with experiences in the basic, clinical and epidemiologic sciences. (8) Development of a community outreach program in cancer to 8 community hospitals, with specialized programs of education aiming at medical staff, community nurses and social workers. (9) Opportunities for community physicians and oncologists to enter their patients into protocols of study and treatment developed either by the medical center or the national studies in which the center participates. (10) Assisting community hospitals with the development of resources to improve the management of cancer patients at the community level, including establishment of tumor registries and oncology clinics, seeking to qualify for approval of their cancer program by the American College of Surgeons, and assistance with participation in protocol treatment studies. (11) Development of coordinated programs of research and education with the Hubert H. Humphrey Cancer Research Center at Boston

Program Director: Margaret H. Edwards, M.D.

University. (12) Recruitment of staff from the departments of psychiatry and biosocial sciences to participate in demonstrations of the psychologic and psychosocial needs of cancer patients. (13) Development of evaluation instruments to measure the effectiveness and acceptance of the projects and activities developed by this program.

Plans: The program is planning to establish new educational opportunities for students focusing on psychosocial aspects of a cancer diagnosis and on the use of tumor registries in cancer education. Through the community hospital outreach program, new educational activities will be aimed at physicians, the allied professions and the public, to gain their acceptance of currently available methodologies in early cancer diagnosis and modern approaches to treatment. Also, further projects aimed at improving evaluation methodologies will be undertaken.

Grant 18039: Clinical Cancer Education Program

From 07/01/75 to 06/30/85 FY 81: \$76,824
Dr. John R. Hartmann, Childrens' Orthopedic Hospital
Seattle, Washington, 98105

Objectives: To develop a model clinical cancer education program for clinical associates, house staff, practicing physicians, nurses, social work students, and other paramedical personnel in pediatric oncology. An elective for medical students is heavily subscribed; the maximum participation is two per month. Individual didactic sessions are given twice weekly, in addition to a daily 8 a.m. one-hour conference. Currently an undergraduate medical student is working with Dr. Bleyer on the pharmacokinetics of methotrexate. The weekly Tumor Board has expanded with the participation of 20-30 physicians and paramedical personnel. Presentations are given to practicing physicians throughout the Washington, Alaska, Montana and Idaho area.

Accomplishments: Currently one and usually two medical students, two to three interns (PL-1), one resident (PL-2 or - 3), clinical associates and one senior attending comprise the ward team which supervises the care of 15-20 inpatients at all times. Wednesday morning guest lecturers from the greater Seattle area present topics in hematology, oncology, radiotherapy, nuclear medicine, bone marrow transplantation, basic immunology, molecular biology and the like. Currently two former clinical associates on this grant are involved in the research training program: Dr. Robert Andrews works on monoclonal antibody production with Dr. Irwin Berstein, and Dr. Frank Balis works on methotrexate pharmacokinetics with Dr. W. Archie Bleyer. Evaluation of the program is done in monthly conferences with the clinical associates in addition to the others; written evaluation by both students and house staff of their rotation on this service and further evaluation by Dr. James Clark is done on an ongoing basis.

Plans: We will continue to fulfill the basic objectives through the intensive training and care of over 600 children with malignant disease, approximately 80% of which are on Childrens Cancer Study Group protocols. In 1981 we shall have three clinical associates despite the reduction of funding on this grant; two will be supported by partial funding on this grant and one from other sources, in addition to partial support from the American Cancer Society. A strong program for parent and patient education has been developed by Ms. Laurie Rudolph and Dr. Thomas W. Pendergrass intitled, "Coping with Childhood Cancer". The program is being considered for nationwide implementation through the American Cancer Society. We anticipate continuing active in-depth participation with the Childrens Cancer Study Group, epidemiologic studies, pharmacokinetic studies for methotrexate, and the application of monoclonal antibodies to differentiation surface antigens in various types of leukemia. In addition an APPLE II computer was recently installed in the Division for the development of epidemiologic studies, didactic self-teaching computer courses and the like.

Program Director: Margaret H. Edwards, M.D.

Grant 18067: Clinical Cancer Education Program

From 07/01/75 to 06/30/84 FY 81: \$51,689
Dr. Robert J. Faulconer, Eastern Virginia Medical School
700 Olney Road, Norfolk, Virginia 23507

Objectives: The program is developed to provide: (1) a unified cancer education program within a regional geographic network commencing with first year medical students in a three-year curriculum with continuation through appropriate clinical clerkships, and to residency programs and continuing medical education programs for medical practitioners, nurses and allied health professionals; (2) a teaching syllabus and computerized self-assessment/instructional program, adaptable to beginning students' needs and having the flexibility to provide advanced and current information for experienced practitioners in the various fields of oncology. This system is to be made available within the regional network by location of computer terminals in the Eastern Virginia Medical School and in key hospitals.

Accomplishments: (1) Establishment of the Tidewater Regional Cancer Network, the Cancer Program of the Eastern Virginia Medical Authority and the Eastern Virginia Medical School, through which the Clinical Cancer Education Program is administered. (2) Established outreach program of Visiting Tumor Boards for hospitals in Eastern Virginia including: U.S. Public Health Service Hospital, Norfolk; Northampton-Accomac Memorial Hospital, Nassawadox; Louis Obici Memorial Hospital, Suffolk; Norfolk Community Hospital; Chesapeake General Hospital. (3) Provision of regularly scheduled lectures by visiting professors of clinical oncology in the medical school and in community and federal hospitals in Eastern Virginia. (4) Sponsorship of the first statewide cancer research seminar (basic and clinical) ever held in Virginia (March, 1981). (5) Publication of an oncology syllabus written by faculty of the Eastern Virginia Medical School. (6) Activation of a computerized self-assessment/instructional program for clinical oncology with terminals in four area hospitals. (7) Introduction of a unique month-long segment of instruction in clinical oncology and hematology for medical students completing basic science and about to enter clerkships. (8) Program evaluation through annual item analysis performance in neoplasia with cooperation of the National Board of Medical Examiners. (9) Provisions of annual student cancer conferences at the EVMS featuring nationally recognized oncologists. (10) Establishment of an oncology nursing continuing education program fulfilling a critical community need. (11) Presentation of seminars for clergy developing the role of clergy as members of the cancer management team. (12) Presentation of a public forum on breast cancer.

Plans: For the coming year the principal effort will be directed to a total revision of the EVMS Oncology Syllabus based on needs for updating and increasing its utility that became evident during current use. The self-assessment/instructional package based upon computerized oncology data will be expanded considerably and a mechanism developed to evaluate the package as well as evaluate users' performance. Work will begin on adapting the undergraduate oncology teaching program to the four year curriculum which will be activated in 1983. The number and scope of visiting and outreach education programs will be expanded.

Program Director: Margaret H. Edwards, M.D.

Grant 18107: Clinical Cancer Education Program

From 07/01/77 to 06/30/82 FY 81: \$19,474

Dr. Philip A. DeSimone, University of Kentucky College of Medicine
800 Rose Street, Lexington, Kentucky 40536

Objectives: The Clinical Cancer Education program purports to improve the quality of Cancer Education and ultimately cancer care by (1) developing new comprehensive cancer education programs while (2) expanding existing programs for the University of Kentucky College of Medicine. A multidisciplinary exposure to the positive aspects of cancer diagnosis, treatment and management within the preclinical medical school curriculum will facilitate student and physician attitudes toward cancer and their effectiveness in patient care. The provision of Cancer Learning resources and related continuing cancer education activities serves the medical student body in acquisition of cancer data and the professional medical community in practice.

Accomplishments: (1) Organization and conduct of the medical school elective course "Clinical Studies in Cancer" and measurement of course impact on student attitudes towards cancer; (2) implementation and evaluation of a Cancer Attitude Survey for the University of Kentucky College of Medicine faculty and housestaff, including publication of the results in the medical literature. (3) Development and maintenance of the Cancer Learning Center including expansion of both inventory (cancer literature) and facilities (equipment, instructional resources). (4) Organization and conduct of the Oncology Lecture Series with thematic emphasis upon cancer prevention, the role of cancer epidemiology, cancer screening, detection, and clinical nutrition. The Oncology Series has expanded both medical grand rounds and clinical conferences with the Medicine/Hematology/Oncology housestaff. Broadened Oncology Series promotion resulted in attracting a significant percentage of the non-academic medical community and increased interest from other College of Medicine departments. (5) Implementation of statewide Needs Assessment for clinical cancer education of primary care physicians. This project has been conducted jointly with the University of Kentucky Cancer Network Outreach division and is expected to reveal the status of Kentucky practitioners' knowledge and deficiencies in cancer diagnosis and treatment.

Plans: The University of Kentucky Medical College Clinical Cancer Education Program will continue all major ongoing projects, including didactic cancer instruction, enhancement of Cancer Learning Center resources, and coordination of the Oncology Lecture Series. Several cancer conferences for practitioners are scheduled or anticipated beyond the University environment, based upon the ongoing needs assessment data. Added focus is expected for program evaluation with increased direct input from community oncologists and practitioners in planning future cancer education activities.

Program Director: Margaret H. Edwards, M.D.

From 07/01/75 to 06/30/84 FY 81: \$62,420

Dr. Eugene P. Frenkel, University of Texas Health Science Center at Dallas,
Southwestern Medical School, 5323 Harry Hines Blvd., Dallas, Texas 75235

Objectives: The program focuses on the development of multidisciplinary education in clinical oncology as a continuum extending from the medical student activities through postgraduate training to an educational base for community physicians. The medical student program points toward a vertical core with emphasis on the natural history of neoplasia and current modes of study, diagnosis and therapy, with the use of multidisciplinary units as role models. Special student programs designed for those interested in a career in an oncology-related area provide opportunities for extended (2-4 months) experience (clinical assistant program) on a tutorial basis as an integral part of an oncology clinical team. Another program promotes multidisciplinary activities for candidates interested in family practice and emphasizes the critical aspect of their role in "early decision-making" and related cancer control. Graduate educational activities focus on interdisciplinary "site" tumor conferences, diagnostic and therapeutic advances, and the role of the clinician in cancer control. Specialized opportunities are provided for candidates interested in a career in an oncology discipline, and the entire clinical program is interdigitated with the graduate program in cancer immunology. In addition, the program extends an educational base to most of the community hospitals in the North Texas area.

Accomplishments: Through the activities of the program, multidisciplinary "site" tumor conferences have been developed for most of the major tumor sites. These teams have then been used as the teaching model for the students and a clinical core model for the graduate program (house staff and practicing physicians). The development of a clinical assistant program has given multiple types of opportunities for in-depth exposure of students to areas of cancer detection and all facets of therapeutic management of the patient. We developed an outreach program to link the Medical School activities to the family practice training programs and are beginning to use that program as a cancer control model. We have developed an Oncology Learning Center to provide a focus for student and house-staff candidates, as well as a resource for community-based physicians. The development of an area-wide hospital-linked closed-circuit T.V. Network has provided the matrix for a regular continuing education program for the physicians in the North Texas area.

Plans: These include: (1) broadening the existent "site" tumor conference units to include other body systems, improving their base, increasing their scope, and extending these model units into the community as a service activity; (2) continuing the development of a core vertical track in oncology for the medical students; (3) improving the clinical assistants' program to provide a broader base of clinical associate candidates into cancer control; (4) implementing new programs in psychiatry and "social" oncology to expand the care base provided and to enhance the educational recognition of the extended needs of the cancer patient; and (5) expanding the involvement in the family practice outreach program in the North Texas area.

Program Director: Margaret H. Edwards, M.D.

Grant 18139: Community Based Therapy for Children with Cancer

From 09/01/75 to 08/31/81 FY 81: 0 (Ann. \$114,684)
Dr. C. Thomas Kisker, Medical Laboratories Building, Room 247A
Iowa City, Iowa 52242

Objectives: Iowa's Community Based Therapy for Children with Cancer Project is to provide primary care practitioners with training and consultive services enabling them to demonstrate equal competency in treating children with cancer when compared with pediatric hematologist-oncologists. By sharing patient management, between the oncologist and the private practitioner, the most effective treatment measures are made available to all children at significantly reduced cost. The computer-assisted patient and data management system being developed will help meet the demands of pediatric cancer patients who increasingly are placed on group cancer treatment protocols.

Accomplishments: During 1980, five pediatric hematologists-oncologists cared for 112 pediatric cancer patients and in cooperation with 108 private practice physicians, shared in the management of an additional 164 pediatric patients on cancer treatment protocols.

The quality of care received by the shared management patients is comparable to that received by the specialist management patients with a 40% savings in out-patient costs for the families of patients selecting the shared management system for care.

A major accomplishment has been the development of the first phase of the Iowa Computer-Assisted Patient and Data Management System. The completed system will provide physicians with assistance in treating patients regardless of the complexity of the treatment protocol or its test and medication schedule. A computer printed, date oriented, Test and Medication Schedule for patients on Childrens Cancer Study Group Leukemia protocol 162 is complete. It is a calendared document starting with the patient's date of diagnosis, listing the tests and medications to be performed during each scheduled time the patient is to be seen during each phase of therapy. Computer printed, self-coding, patient and visit specific Encounter Forms are also ready for use with leukemia patients on Childrens Cancer Study Group protocol 162. Each of these calendared Encounter Forms calculates for a specific patient the drug dosage to be administered that day according to body weight or surface area, notes contraindications for each drug and directly collects many of the physician's required observations as a self-coded structured record.

Plans: Completion of project includes: (1) continuing to recruit primary care physicians to participate in shared management; (2) producing computer printed patient Test and Medications Schedules and computer printed, date oriented, self-coding, structured data collection Encounter Forms for specific patients on other Childrens Cancer Study Group protocols.

Program Director: Donald N. Buell, M.D.

Publications:

Kisker, C.T., Strayer, F., Kwan Wong, Clarke, W.R., Strauss, R., Tannous, R., Janco, R., and Spevak, J.: Health outcomes of a community-based therapy program for children with cancer - a shared management approach. Pediatrics 66:900-906, 1980

Stehbens, J., Ford, M., Kisker, C.T., Clarke, W., and Strayer, F.: WISC-R verbal performance discrepancies in pediatric cancer patients. Jour. of Pediatric Psych. 6:61-68, 1981

Strayer, F.H., Kisker, C.T., and Fethke, C.: Cost-Effectiveness of a shared management delivery system for the care of children with cancer. Pediatrics 66:907-911, 1980

Strayer F.H., Fethke, C.C., Kisker, C.T., DeKrey, N.G.: Physician incentives for a shared management of childhood cancer patients. Pediatrics vol. 67 No. 6, 1981.

Wong, K.Y., Ballard, E.T., Strayer F. H., Kisker C.T., and Lampkin, B.C.: Clinical and occult testicular leukemia in long-term survivors of acute lymphoblastic leukemia. The Jour. of Pediatrics 96:569-574 1980.

From 07/01/75 to 06/30/84 FY 81: \$75,747

Dr. Rose Ruth Ellison, Columbia University College of Physicians and Surgeons
630 West 168th Street, New York, New York 10032

Objectives: The program was designed to expand the oncology education for Clinical Associates in a number of areas: Medical Oncology, Surgical Pathology, Radiation Oncology, and Cancer Epidemiology. The development of a hospital-wide Interdisciplinary Oncology Conference was to be undertaken to provide an appropriate milieu for training a variety of individuals to reach therapeutic decisions in an interdisciplinary fashion.

Accomplishments: New sections have been added to the oncology portion of the Abnormal Human Biology syllabus for a major second-year medical student course. The remainder of the oncology text for this course has been completely revised. A fourth-year elective oncology sub-internship is now available on the Clinical Cancer Research In-patient Facility. A fourth-year pediatric oncology elective has been broadened in its scope. (2) Successful recruitment has taken place in the division of medical oncology with there now being eight full-time faculty members. A new head of pediatric hematology/oncology was recruited and additional recruitment is underway. This has allowed expansion of the program for the Clinical Associates in both of these fields, with improved teaching and new opportunities for clinical and laboratory research in oncology. A new coordinator of surgical oncology has been named and planning for the development of a program in surgical oncology is underway. A new chairman of the department of urology and one of his faculty are planning a program in urologic oncology. (3) The program proposed for training an individual in cancer epidemiology, environmental science, carcinogenesis, and cancer registry functions has provided suitable course material, conferences and field work for this individual as well as opportunities for teaching. (4) The Interdisciplinary Oncology Conference (clinical) has changed its focus while remaining interdisciplinary. The sessions now provide didactic material in surgical, radiation, pediatric and medical oncology with discussions of disease, diagnostic techniques, and treatment. The Tumor Board approach is provided separately by multidisciplinary treatment planning and teaching conferences in a number of areas; these include head and neck cancer, urologic cancer, pediatric cancer, lymphomas, medical oncology and others. Such sessions are attended by medical oncologists, surgical oncologists, surgical specialists, radiation oncologists and pathologists. The Interdisciplinary Conference and the Treatment Planning conferences are supplemented by regular rounds at which cancer patients are discussed and by research oriented sessions.

Plans: Programs already underway in Medical, Pediatric, and Radiation Oncology, Surgical Pathology, and Epidemiology will be continued with increased stress on interdisciplinary approaches. These will be expanded by the development of programs in Surgical Oncology, Urologic Oncology and in Psychiatric Oncology. This educational program will be developed within the frame-work of a proposed multi-disciplinary one-class-care out-patient facility that will provide a focus for teaching medical students, house staff, and Clinical Associates in the fields named.

Program Director: Margaret H. Edwards, M.D.

From 07/01/75 to 06/30/84 FY 81: \$191,742
Dr. Edwin A. Mirand, Roswell Park Memorial Institute
666 Elm Street, Buffalo, New York 14263

Objectives: This program aims to provide and opportunity for undergraduate medical, dental and nursing students, clinical associates, post-graduates, faculty and allied health personnel to broaden their knowledge in the field of oncology. To achieve these goals we offer courses in graduate education, a master's program in oncology, clinical assistantships, and continuing education courses for practicing physicians, dentists, and professional nurses. These courses provide (a) education in cancer patient approach and in cancer management including diagnosis, treatment and rehabilitation, (b) familiarization with newest concepts in etiology, epidemiology and prevention of cancer, and (c) opportunities for basic and clinical cancer research.

Accomplishments: (1) 63 MDs in the final year of their training were entered in the clinical associates program. In addition to their departmental activities these trainees participated in interdepartmental teaching and research activities to gain a comprehensive view of the cancer problem. (2) 131 Clinical Assistants, medical students from 29 medical schools, participated in clinical research and patient management for 8-week periods. (3) A four-track program was established offering continuing education to practicing physicians and dentists. This includes an annual 2-day interdisciplinary symposium on a specific area of oncology with emphasis on the most recent progress in that particular area, and monthly 1-day symposia on advances in oncology in a particular specialty given by individual departments. These presentations include formal lectures, conferences, demonstrations, clinical rounds, etc.; 200 guest lecturers were invited to participate. The Visiting Physicians' Program provides an opportunity for practitioners to participate in the clinical activities of a specialty area of their choice at the Institute. An intensive course in General Oncology is designed to provide physicians and dentists with an up-to-date review of the present status of cancer research, covering etiology, pathophysiology, natural history of the disease, biochemical and cytological changes in the cancer patient, and the general problems which the physician faces in cancer patient management. (4) Various nursing programs that were developed include: a graduate program for nurses with a Bachelor's degree to earn a Master's degree in Interdisciplinary Sciences with a specialty in Oncology, and continuing education courses in Oncology Nursing consisting of symposia, seminars, workshops and short-term courses.

Plans: We will continue the programs described above. Theses are continuously evaluated and up-graded on the basis of experience and feedback from participants. Clinical Associates and Clinical Assistants are being accepted for the coming year. Programs for continuing medical and nursing education are planned two years in advance. In-service training for nurses is expanded to include new approaches in cancer management.

Program Director: Margaret H. Edwards, M.D.

From 07/01/75 to 06/30/84

FY 81: \$81,242

Dr. Ernest C. Borden, Wisconsin Clinical Cancer Center

600 Highland Avenue, Madison. Wisconsin 53792

Objectives: The program is designed to improve cancer-related teaching and learning materials for medical students ensuring that all phases of cancer intervention, from prevention through rehabilitation, are included. Another goal is to provide summer experience which will increase medical students' understanding of the multidisciplinary nature of cancer care and research. For pre- and postdoctoral students the intent is to increase awareness of the challenges and opportunities in these areas. For medical graduates at or beyond the PD4 level, improvement in the two-year study program is designed to provide fundamental knowledge of tumor biology, an interdisciplinary background in cancer management, and attitudinal and technical skills essential to optimal care of patients with cancer.

Accomplishments: This year, (1) annual curriculum review of all medical school oncology courses has resulted in addition of content (causative and preventive aspects of oncology, radiation biology and therapy) and expansion of teaching time for the Year II neoplastic diseases curriculum. (2) Year IV electives in ambulatory, inpatient, and preventive oncology have been developed in addition to the 13 other electives with major oncology content. (3) Sixteen pre-Year I and II summer assistants were supported to work with individual faculty mentors in a variety of in-depth clinical cancer research experiences. These students arranged weekly seminars in relation to their areas of concentration. (4) The grant has supported six clinical associates at various levels of post-graduate training; particularly notable has been the development of programs in surgical oncology and pathologic oncology. All subspecialty programs have been redesigned to require multidisciplinary rotations. (5) In collaboration with Dr. Howard Stone of the Office of Educational Resources, evaluation has been carried out for each supported activity. (6) Regional and specialty conferences for continuing education of practicing physicians have been carried out. Likewise, the medical oncology visiting fellow program has offered four practicing physicians the opportunity to spend a week at the Clinical Oncology Division of the WCCC. (7) A cancer newsletter has been sent to about 100 practicing physicians on a quarterly basis. It is expected to become a monthly letter within the next year.

Plans: The Year II neoplastic diseases course will have four additional hours (up from 19), permitting content regarding common cancers to be added. The summer assistantship program will be continued and a survey of previous assistants will be conducted to ascertain potential impact upon specialty choice. New associate programs in urologic oncology and radiation oncology, as well as continuing programs in surgical oncology and pathologic oncology, will be developed with increased multidisciplinary rotations. Development of a course in cancer diagnosis and management for primary care physicians will be undertaken. CME conferences and individualized visiting fellowships will be continued.

Program Director: Margaret H. Edwards, M.D.

Grant 18410: Tumor Antigens in Pancreatic Cancer

From 04/01/76 to 03/31/82

FY 81: \$106,217

Dr. T. Ming Chu, Department of Diagnostic Immunology Research and
Biochemistry, Roswell Park Memorial Institute, Buffalo, New York 14263

Objectives: The objective of this research project is to identify, isolate and characterize proteins associated with and/or specific for human pancreas cancer. In addition, development of immunodiagnostic reagents and procedures as well as evaluation of these new modalities for detection and monitoring of pancreas cancer are to be studied. Several specific aims, therefore, are set for reaching this goal: development of sensitive immunoassay, such as enzyme-linked immunoassay, for the newly isolated human pancreas histotypic antigen and their clinical evaluation on serum monitoring (similar study will be conducted for the pancreas cancer associated antigen, after refinement of the antiserum reagents); development of immunoperoxidase techniques for tissue localization of these two pancreas antigens; further study on the plasma membrane preparations of human pancreatic tumor; application of a newly developed technique for dissociation of immunoreactive antigen and antibody components; characterization of our pancreatic tumor cell lines; establishment of human pancreatic tumor xenograft using our new pancreatic tumor cell line AsPC-1; in vitro and in vivo morphologic characterization of this new pancreatic adenocarcinoma line; and differential localization of human pancreas associated antigen and carcinoembryonic antigen in homologous pancreatic tumor xenograft.

Accomplishments: Several significant accomplishments have been made from this study during the year. A pancreas cancer associated antigen has been identified and isolated from malignant ascites fluid of pancreatic cancer. This human pancreas cancer associated antigen is a macromolecular glycoprotein and has been characterized biochemically and immunologically. An immunoassay has been developed for measurement of this antigen in serum. Initial clinical evaluation indicated that an elevated level of antigen was detected predominantly in patients with pancreas cancer and shown to be correlated with the extent of disease. By immunocytochemical technique, this antigen was found in tissues derived from adult pancreas cancer, fetal pancreas and some tissues of gastrointestinal origin. A new human pancreatic tumor cell line, AsPC-1, isolated from ascites fluid of pancreatic cancer, has been established in vivo in athymic mice. With the use of this homologous pancreatic tumoral xenograft, many investigations on pancreas cancer now can be initiated, such as the study of antigenic expression, radioimmunolocalization and immune-specific chemotherapy of pancreas cancer. A pancreas specific antigen also has been isolated from human pancreas. This is a pancreas acinar cell specific protein with a molecular weight of 45,000, which has been shown to be secreted in pancreatic juice in large quantity. Although its role in exocrine pancreatic cancer remains to be determined, the biologic importance of this protein in endocrine physiology of the pancreas may be of great importance. New techniques to the isolation and characterization of pancreas cancer-associated soluble immune complexes have also been established.

Plans: We plan to develop a sensitive immunologic assay for the newly identified pancreas specific antigen, as preliminary data have indicated

Program Director: William E. Straile, Ph.D.

that it is present in the serum of pancreatic cancer patients. Production and characterization of monoclonal antibodies to purified pancreas cancer associated antigen is also to be carried out. Data available seem to reveal that the molecule contains a pancreas tumor specific site(s). In addition, with the use of our new pancreatic tumor cell line, production of monoclonal antibodies to AsPC-1 cell surface antigens is to be performed, which in turn will be employed in isolation of plasma membrane preparation associated with pancreas cancer.

Publications:

Chu, T. M., Holyoke, E. D., Douglass, H. O.: Tumor antigens as related to pancreatic cancer. J. Surg. Oncol., 13:207-214, 1980.

Maidment, Jr., B. W., Papsidero, L. D., Chu, T. M.: Isoelectric focusing-- A new approach to the study of immune complexes. J. Immunol Methods, 35:297-306, 1980.

Maidment, Jr., B. W., Papsidero, L. D., Nemoto, T., Chu, T. M.: Isoelectric focusing analysis of soluble immune complexes bound to Protein A-Sepharose. Anal Biochem (In press).

Shimano, T., Loor, R. M., Papsidero, L. D., Kuriyama, M., Vincent, R. G., Nemoto, T., Holyoke, E. D., Berjian, R., Douglass, H. O., Chu, T. M.: Isolation, characterization and clinical evaluation of a pancreas cancer associated antigen. Cancer 47: 1602-1613, 1981.

Grant 18429: Studies of Long-Term Survivors of Childhood Cancer,
Sidney-Farber

From 09/01/75 to 02/29/81 FY 81: 0 (Ann. \$217,300)
Dr. David Nathan, Sidney Farber Cancer Institute, 44 Binney Street
Boston, Massachusetts 02115

Objectives: The objectives of this project were to explore the quality of life among the survivors of pediatric cancer and use the data obtained to enhance understanding of the psychosocial impact of childhood malignancy over the long term. The study focused on patients listed in the Sidney Farber Cancer Institute Long-Term Survivor Registry. Each patient selected for study was at least five years post diagnosis, cancer-free and off of treatment protocols for at least one year. Patient, parent, and sibling interviews of a psychosocial nature were conducted.

Accomplishments: At the time of termination the project staff had interviewed more than 117 pediatric cancer survivors ranging in age from 6 to 37 years. Many parents and siblings of these patients were also interviewed. A number of factors were identified as being positively related to favorable psychosocial adjustment over the long term including onset of cancer early in life, extended periods of remission, absence of relapses, high intellectual functioning, good social maturity, and higher-than-average socioeconomic status. Approximately 47 percent of the long-term survivors interviewed demonstrated residual psychosocial sequelae ranging from mild anxiety and depression to substantial difficulty in holding a job or functioning effectively in school or the family. The ability to avoid or deny worries about recurrence of disease seems critical to maintaining adequate long-term adjustment. Detailed data on family processes, recollections, and coping strategies were also recorded. Evidence of significant discrimination against the pediatric cancer survivor who later seeks employment or insurance (health or life) was also noted. The period of the project covered by this report included final data analyses and preparation of terminal publications on the four and one-half year project.

Plans: The project is ended. No new psychological studies of the long-term survivor population are proposed, although a psychotherapy intervention project has been designed to assist current patients using data gleaned from this project to design the new program.

Publications:

Gogan, J.L., Koocher, G.P., Fine, W.E., Foster, D.J., and O'Malley, J.E.: Surviving childhood cancer and marriage: Issues affecting adult adjustment. Amer. Jour. of Orthopsychiatry. 49:423-430, 1979.

O'Malley, J.E., Foster, D.J., Koocher, G.P., and Slavin, L.A.: Visible physical impairment and psychological adjustment among pediatric cancer survivors. Amer. Jour. of Psychiatry. 137:94-96, 1980.

Program Director: Sandra M. Levy, Ph.D.

From 05/01/76 to 04/30/81 FY 81: 0 (Ann. \$156,549)
Dr. Emil Berkanovic, University of California, School of Public Health,
Los Angeles, California 90024

Objectives: The overall objective of this research is to study the processes underlying (a) the decision to seek medical care for specific symptoms, (b) utilization of health services, (c) compliance with medical service, (d) the effect of care and compliance on subsequent symptom experience, disability and perceived health status. The rationale lies in the importance of early detection for cancer control through the appropriate use of health services and compliance with medical advice. The role of psychological variables is examined in regard to: (1) the decision to seek care for all reported symptoms, symptoms for which medical care is judged appropriate and cancer relevant symptoms and (2) compliance with medical advice.

Accomplishments: Data consist of the symptom experiences of a representative sample of 1,200 metropolitan Los Angeles adults over a one-year period (1976-1977). All analyses from the first interview were completed prior to October 1, 1979. Several published papers, as well as several presented papers, resulted from these analyses. These papers reported data on breast cancer detection behavior, reactions to the mammography debate, the impact of prepayment on preventive medical advice and changes in smoking behavior.

The analysis of the entire data set began about October 1979. All symptoms reported by the respondents during the entire study year were coded on a 4-point scale of cancer relevance by three oncologists at the UCLA Comprehensive Cancer Center. The reliability of these ratings was .73. The same symptoms were coded on a 4-point scale of necessity of medical attention by three primary care physicians. Reliability for these ratings was .76.

Preliminary analyses have been conducted of use of physician services for all symptoms and those judged to be cancer relevant. These analyses accounted for 58 percent of the variance in use of physician services, respectively. The major predictor variables were: (a) advice given by friends and family, (b) perceived seriousness of the symptom, and (c) perceived efficacy of medical care in relieving the symptom. Both analyses are encouraging to the extent that these predictor variables can be affected through health education. The magnitude of the task for health education, however, is illustrated by the findings that only 50 percent of the people with cancer relevant symptoms perceived them to be serious and only 60 percent thought a visit to the physician would be efficacious.

Program Director: Rosemary Yancik, Ph.D.

Publications:

Berkanovic, E.: The effect of inadequate language translation on Hispanics' responses to health surveys. Am. J. Pub. Hlth. 70(12):1273-1276, 1980.

Berkanovic, E. and Reeder, S.J.: Awareness, opinion and behavioral intention of urban women regarding mammography. Am. J. Pub. Hlth. 69(11):1172-1174, 1979.

Berkanovic, E., Telesky, C. and Reeder, S.: Structural and social psychological factors in the decision to seek medical care for symptoms. Med. Care. (in press).

Jordan, L.A., Marcus, A.C. and Reeder, L.G.: Response styles in telephone and household interviewing: A field experiment. Pub. Opin. Quarterly. 44:210-222, 1980.

Marcus, A.C.: Mode of payment as a predictor of health status, use of health services, and preventive health behavior: A report from the Los Angeles Health Survey. Med. Care. (in press).

Marcus, A.C., Reeder, L.G., Jordan, L.A. and Seeman, T.E.: Monitoring health status access to health care, and compliance behavior in a large urban community. Med. Care. 18(3):253-265, 1980.

Marcus, A.C. and Seeman, T.: Sex differences in health status: A reexamination of the nurturant role hypothesis. Am. Soc. Rev. 46:119-123, 1981.

Marcus, A.C. and Seeman, T.E.: Sex differences in reports of illness and disability: A preliminary test of the "fixed role obligations" hypothesis. J. Hlth. Soc. Behav. (in press).

Reeder, S., Berkanovic, E. and Marcus, A.C.: Breast cancer detection behavior among urban women. Pub. Hlth. Reports. 95(3):276-281, 1980.

Grant CA 18510: Cancer Center Community Outreach Development Grant

From 02/01/77 - 03/31/83

FY 81: \$504,310

Dr. Jack E. White, Howard University Cancer Center, 2041 Georgia Avenue, N.W.
Washington, D.C. 20060

Objective: The overall objective of the Howard University Cancer Center Outreach Program is to reduce cancer mortality and morbidity in the Washington, D.C. area population through: (1) careful assessment of the cancer experience among Washington area residents, (2) dissemination of appropriate information on primary and secondary cancer prevention to both the lay public and professional communities, and (3) development of collaborative cancer-control efforts among organizations and institutions in the Washington, D.C. area.

The program's specific aims are (1) to collect and analyze descriptive cancer-related data on the population of the Washington, D.C. area in order to identify specific cancer problem areas and high risk sub-populations and to formulate epidemiologic hypotheses for further examination and testing. (2) to develop and implement targeted health education and information dissemination programs in order to inform area residents about cancer risk factors and the benefits of and facilities for early cancer detection. (3) to help coordinate current cancer-control activities in the Washington area and assess the need for new activities by assessing current education, screening, and detection programs and facilities; providing technical assistance to appropriately augment current cancer-control activities; and providing coordination among area researchers, administrators, and other parties interested in cancer control. (4) to identify mechanisms for initiating appropriate additional cancer control activities and programs by identifying specific needs; providing viable solutions to meet needs; and making needs and solutions known to local organizations and governmental agencies so that they can respond by delivering either funds or actions.

Accomplishments: Significant accomplishments included the following: (1) Data collection and analysis: descriptive and analytic studies have focused on further specification of the cancer risk by site, compilation of incidence and survival rates for District residents, and identification of specific causative factors related to the high local cancer rates.

A series of six site-specific reports on the cancer incidence, distribution and survival patterns of patients in metropolitan Washington is being produced in conjunction with the District's Department of Human Services. These reports will focus on cancer of the esophagus, breast, lung, prostate, colon-rectum, and "all other sites."

(2) Health Education: The Cancer Education Curriculum for the D.C. Public Schools was implemented in grades kindergarten through twelve. Two training sessions for teachers were held in November 1980 and June 1981, respectively. The Outreach Program's Speakers Bureau conducted sixty-eight community programs on the subject of cancer. This health information thrust was assisted by the Cancer Center's continued operation of its cancer information service (CIS), which received its 15,000th call in March 1981.

Program Director: Carlos E. Caban, Ph.D.

(3) Collobarative activities: (a) assisted in the further restructuring of the Metropolitan Washington Regional Cancer Registry in order to produce improved reports on specific cancer sites (b) collaborated in epidemiologic and biostatistical activities with the Maryland Department of Health and Mental Hygiene, the Baltimore City Health Department , and the Johns Hopkins University, (c) initiated activities that will lead to an improved psycho-social/physical program for cancer patients at Howard University Hospital, (d) formalized linkage with the Cancer Center's Clinical Branch through the appointment of a half time clinician to the Outreach Branch staff.

(4) Evaluation: The evaluation of all program activities has been strengthened by the creation of a Planning and Evaluation Committee. All prospective projects must be reviewed by this committee for soundness of design prior to implementation.

Plans: The Outreach Program of the Howard University Cancer Center plans to maintain and strengthen its current activities. Additionally, considerable efforts will be undertaken in the clinical cancer control and psycho-social areas. These activities will be done in conjunction with the Vincent T. Lombardi Cancer Center at Georgetown University which with the Howard University Cancer Center comprises the Comprehensive Cancer Center for this region. New and expanded public health education activities are also planned for Washington's Service areas 6, 5, and 3, where cancer mortality is among the highest in the city.

PUBLICATIONS

White, JE; Askey, DA: Prevention...An Alternative Solution. Cancer Education Curriculum for Elementary and Secondary Schools, 1980.

White, JE; Enterline, JP; Alam, Z; Moore, RM: Cancer Among Blacks in the United States -- Recognizing the Problem. Mettlin, CJ; Murphy, GR (eds): Cancer Among Black Populations. New York, Alan R. Liss, Inc., 1981.

Grant 18625: Production of Rats with Isologously Transplanted R3327

From 06/30/76 to 04/30/82

FY 81: \$76,391

Dr. Norman H. Altman, Papanicolaou Cancer Research Institute, 1155 N.W. 14th Street, Miami, Florida 33136

Objectives: The availability of suitable animal models is essential for the study of prostate cancer. These models allow us to investigate basic biological characteristics, early diagnostic techniques and various treatment modalities. We maintain breeding colonies of Copenhagen and Fischer rats to serially propagate R3327. This is a slow-growing, hormone responsive, well differentiated prostatic adenocarcinoma which is an excellent model for the human disease. Our major objectives are to maintain and characterize this tumor which we supply to qualified investigators.

Accomplishments: We have been able to maintain the important biological characteristics of R3327 through 29 transplant generations spanning 20 years. This has been accomplished by a careful, detailed quality assurance and monitoring program. We have provided rats implanted with tumors or frozen tumor material to 51 investigators in 28 different institutions. This resource allows investment to plan and complete pilot research programs in a minimum amount of time. Without this resource new programs would be costly and take six to twelve months to complete since R3327 is such a slow-growing tumor. We are currently involved in a collaborative research program with four other laboratories to define the acceptable limits for the biological and morphological characteristics of R3327.

Plans: We will continue to maintain the breeding colonies of rats and to closely monitor each transplant generation of R3327 to insure a uniform, reproducible model for prostatic cancer.

Publications: None.

Program Director: Andrew Chiarodo, Ph.D.

From: 09/01/75 to 12/31/82 FY 81: \$60,843
Dr. Hiromu Matsumoto, University of Hawaii, 1800 East-West Rd, Honolulu, HI 96822

Objectives: Methylazoxymethanol (MAM)-glucoside and MAM-glucuronide orally administered are hydrolyzed by bacterial glucosidase and glucuronidase respectively to yield the common aglycone, MAM - whereas glucuronide induces primarily colon tumors the glucoside induces mostly kidney tumors. The reasons for the difference in site specificity of the two glycosides are being investigated. The carcinogenic and biochemical effects of MAM, and two of its glycosidic conjugates, MAM-glucoside (cycasin) and MAM-glucuronide, colon carcinogens of varying effectiveness, will be compared.

Accomplishments: Equimolar quantities of MAM-glucoside (cycasin) and MAM-glucuronide were orally administered to young and mature male rats either once or once a week for four weeks. The animals are killed and autopsied as they begin to lose weight rapidly or show signs of anal bleeding. A simple procedure for the determination of methylated purines in urine using high pressure (performance) liquid chromatography is being developed in order to compare the relative methylating effectiveness of MAM-glucoside and MAM-glucuronide. When O^6 -methylguanine is injected into rats, it is recovered almost quantitatively. No O^6 -methylguanine is detected in the urine when MAM-acetate is injected at several dosage levels into male rats. The results thus far indicate that the quantity of O^6 -methylguanine excreted in the urine after the injection of the methylating agent, MAM-acetate, is below the detectable nanomole range of the procedure, or that the O^6 -methylguanine formed on the deoxyribonucleic acid (DNA) is demethylated in the cell. Tritium labelled MAM-acetate has been injected intravenously into rats and after 24 hours the animals were killed and the colon removed and washed. The colon is cut into one cm sections and the mucosa is dissolved and the radioactivity counted. There are two areas of high radioactivity. Thirty-six rats injected with MAM-acetate developed tumors mostly in the areas of high radioactivity. The areas of high radioactivity indicate that there is some sort of concentrating mechanism operating. Autoradiographic study of the tritium labelled colon tissue is being carried out.

Plans: Examination will be completed on all animals orally administered MAM-glucoside (cycasin) and MAM-glucuronide. The presence of O^6 -methylguanine and 3-methyladenine in urine of rats injected with methylating carcinogens other than MAM will be examined. Quantities of cycasin and MAM-glucuronide excreted in the urine of rats orally administered those compounds will be determined. Free MAM will be prepared and MAM- α -glucoside will be prepared and tested on tumor α -glucosidase.

Publications:

Matsumoto, H., Takata, R.H., and Ishizaki, H.: Determination of the Carcinogen Methylazoxymethyl- β -D-glucosiduronic acid in rat bile and urine. J. Chromatog., in press.

Program Director: Vincent J. Cairolì, Ph.D.

Grant 18643: Experimental Chemotherapy of Murine Bladder Cancer

From 06/01/75 to 05/31/84

FY 81: est. \$158,992

Dr. M.S. Soloway, University of Tennessee Center for the Health Sciences,
Memphis, Tennessee 38163

Objectives: The objectives include screening single and combination chemotherapeutic agents for antineoplastic activity in both primary and transplanted FANFT induced bladder cancer. We have been able to grow some of these tumors in vitro using the tumor colony assay system. We hope to simultaneously compare growth inhibition by chemotherapy in this system to the responsiveness of the same tumor to various drugs in vivo.

We are continuing our investigation of the effectiveness of various drugs used by the intravesical route for their ability to prevent or alter the development of primary FANFT-induced tumors.

Accomplishments: During the past year several drugs have been tested for their ability to inhibit the growth of transplanted bladder tumors: AMSA, maytansine, VP16, methyl-GAG, methotrexate, Adriamycin and several platinum analogs. Anguidine and DDP were compared using the transplanted tumor MBT-8. Anguidine significantly reduced tumor growth compared to the controls however the ILS was only 8%. DDP was far superior, 46% ILS.

DDP and JM-9 were tested in a similar manner. Both significantly reduced tumor growth ($p < 0.01$); however, DDP had a greater ILS (45% vs. 31%). In a subsequent study both DDP and bleomycin reduced tumor growth ($p < 0.001$). Once again, DDP proved to be the most effective drug with an ILS four times that of bleomycin (32% vs. 8%). Bleomycin used in combination with DDP further reduced tumor growth with a slightly better ILS than DDP alone (38% vs. 32%).

DDP and Adriamycin were tested singly and in combination using the MBT-2 tumor line. Both drugs reduced tumor growth ($p < 0.001$). The ILS for mice receiving DDP was almost double that of Adriamycin (40% vs. 22%). The combination of DDP and Adriamycin further inhibited tumor growth, however the ILS was not improved.

Five of these drugs were tested as single agents on FANFT induced primary tumors. Therapy was initiated after 24 weeks on FANFT (Day 0). Drugs were given weekly for four weeks. Bladders were removed week 49.

None of the drugs significantly reduced the incidence of tumors when compared to the controls, 88%. The presence of a few very large bladder tumors in mice treated with AMSA or maytansine raised the mean bladder weight to 154.0 and 88.0 mg., respectively, control = 69.0 mg. The group receiving bleomycin had a mean bladder weight of 53.5 mg. JM-9 effected a significant reduction in the mean bladder weight, 32.5, $p < 0.05$. DDP produced the lowest mean bladder weight, 19.0.

During the period of this grant, a series of experiments have been performed to evaluate the morphologic changes related to topical chemotherapy. The effect of thio-tepa on normal and abnormal urothelium was initially studied. Thio-tepa

Program Director: William E. Straile, Ph.D.

caused increased exfoliation with consequent denudation of normal urothelium when compared to the effects of saline instillation. This effect was transient and was not observed after 48 hours. No other changes could be ascribed to thio-tepa. Similar studies were performed on bladders with dysplasia and carcinoma *in situ*. Cellular degeneration and cytoplasmic vacuolization were observed in both treated and control groups, these changes were slightly more common among the treated animals. More importantly, cells with atypical nuclei which might be confused with malignant tumor cells were rarely observed, occurred in animals treated with both thio-tepa and saline and were virtually confined to the superficial (umbrella) elements.

A third experiment evaluated the inhibitory effect of thio-tepa on tumor growth. Groups of mice on FANFT received multiple doses of either thio-tepa or saline. The incidence of tumors was not reduced by thio-tepa, however the drug did halt the progression of tumors from low-stage and grade to high-stage and grade, and this result was statistically significant. Similar studies with almost identical results have been done using mitomycin C.

Seeding of malignant tumor cells at the time of fulguration of a primary bladder tumor may be an important cause of recurrence. A model system using electrocautery has been designed in our laboratory. We have carried out experiments to determine the optimal time and site of implantation after electrocautery. Implantation is most likely to occur 24 hours after thermal injury; sites removed from the injury can be colonized as well as foci adjacent to the cauterized areas.

Plans: Our future efforts will be directed toward altering the turnover rate of urothelial cells to potentiate the incorporation of antitumor compounds into the cells and enhance their cytotoxic activity. Sequential combination intravesical chemotherapy will be compared to single agent therapy in primary tumors. The other major goal will be to continue the comparison of in vitro with in vivo activity of various drugs. This will determine the ability of the tumor colony assay to screen drugs for activity in TCC.

Publications:

Daskal, Y., Soloway, M.S., DeFuria, M.D., and Crooke, S.T.: Morphologic Effects of Mitomycin C Administration Intravesically to Normal Mice and Mice with N-[4-(5-nitro-2-furyl)-2-thiazolyl] Formamide Induced Bladder Neoplasms. *Cancer Research* 40: 261-270. 1980.

Murphy, W.M., and Soloway, M.S.: The Effect of Thio-tepa on Developing and Established Mammalian Bladder Tumors. *Cancer* 45: 870-875. 1980.

Soloway, M.S., Masters, S.B., and Murphy, W.M.: Cis-platin Analogs and Combination Chemotherapy in the Therapy of Murine Bladder Cancer. In Prestayko, A.W., Crooke, S.T., and Carter, S.K. (Ed.): *Cis-Platin: Current Status and New Developments*. New York, Academic Press. 1980. pp. 345-359.

Soloway, M.S.: Cis-diamminedichloroplatinum (II) in Locally Advanced and Metastatic Urothelial Cancer. In Seeber, S., Schmidt, C.G., Nagel, G., and Achterrath, W. (Ed.): *CISPLATIN Derzeitiger Stand und neue Entwicklungen in der Chemotherapie Maligner Neoplasien*. S. Karger, Basel, München, Paris, London, New York, and Sydney. 1980. pp. 131-140.

Soloway, M.S. and Murphy, W.M.: Chemotherapy of Murine Bladder Cancer. In Oliver, R.T.D., Hendry, W.F., and Bloom, H.J.G. (Ed.): Bladder Cancer - Principles of Combination Therapy. London, Butterworth & Company. 1981. pp. 37-55.

Soloway, M.S.: Rationale for Intensive Intravesical Chemotherapy for Superficial Bladder Cancer. Journal of Urology 123: 461-466. 1980.

Soloway, M.S. and Masters, S.B.: Urothelial Susceptibility to Tumor Cell Implantation - Influence of Cauterization. Cancer 46: 1158-1163. 1980.

Soloway M.S., Ikard, M., and Ford, K.: Cis-diamminedichloroplatinum (11) in Locally Advanced and Metastatic Urothelial Cancer. Cancer 47: 476-480. 1981.

Grant 18660: International Case-Control Study of Bladder Cancer

From 06/01/76 to 11/30/80

FY 81: \$0 (Ann. \$153,666)

Dr. A.S. Morrison, Harvard School of Public Health, Boston, Massachusetts

Objectives: The primary objective of this project was to evaluate the relation between coffee drinking and the development of bladder cancer. Secondary objectives were to assess the risk of bladder cancer associated with use of artificial sweeteners, with smoking cigarettes and other forms of tobacco, and with employment in certain occupations, and to evaluate the relation of bladder-cancer histology to demographic characteristics and bladder-cancer risk factors.

Broadly-based series of cases and series of controls drawn from the general population of each area were assembled and interviewed in Boston, USA (587 cases, 528 controls), Manchester, UK (541 cases, 725 controls) and Nagoya, Japan (289 cases, 586 controls). Compared to drinkers of an average of less than one cup of coffee per day, those who drank more had a relative risk of bladder cancer estimated as 1.0 (0.8-1.2, 95% confidence interval). With adjustment for cigarette-smoking habits, only small and irregular changes in risk were seen with increasing frequency of coffee consumption. A history of use of artificial sweeteners was not associated with an over-all elevated risk of bladder cancer in any of the study areas, nor did the risk of bladder cancer increase consistently with frequency or duration of use of artificial sweeteners. In each study area, cigarette smokers had about twice the bladder cancer rate of non-smokers, and the risk increased with increasing consumption. Smokers of two or more packs per day who inhaled deeply were at especially high risk. Ex-smokers had a relative risk between that of non-smokers and light smokers. Among subjects who had never smoked cigarettes, pipe smokers were at elevated risk of bladder cancer. In Boston, an elevated risk of bladder cancer was observed in subjects with a history of employment involving dye, leather, paint, organic chemicals, and fuel gas. There were few clear associations of occupation with risk of bladder cancer in Manchester and Nagoya. Pathologic characteristics of bladder cancer were generally similar among the study areas, between the sexes, and between smokers and non-smokers. The histologic grade (degree of malignancy) increased with age and there was a corresponding increase in the proportion of tumors showing submucosal invasion.

Publications:

Friedlander, E., and Morrison, A.S.: Urinary Tryptophan Metabolites and Cancer of the Bladder. J. Natl. Cancer Inst. In Press, 1981

Hoar, S.K., Morrison, A.S., Cole, P., and Silverman, D.T.: An Occupation and Exposure Linkage System for the Study of Occupational Carcinogenesis. J. Occ. Med. 22:722-726, 1980

Program Director: William E. Straile, Ph.D.

Morrison, A.S., and Cole, P.: Urinary Tract. In Schottenfeld, D., and Fraumeni, J.F. (Eds.): Cancer Epidemiology and Prevention. Philadelphia, Saunders, In Press 1981.

From 07/01/77 to 06/30/84

FY 81: \$43,394

Dr. Louis R. Guerra, Louisiana State University, School of Dentistry
1100 Florida Avenue, New Orleans, Louisiana 70119

Objectives: The objectives of this program are: to improve the status of patients through the education and training of health professionals and the general public; to provide classroom instruction to undergraduate, graduate dental students, and dental hygiene students; to provide patient contact to undergraduates, graduate dental students, and dental hygiene students; to provide clinical extramural experiences in the diagnosis, treatment and rehabilitation of head/neck cancer patients; to provide readily available core audiovisual and reference materials; to develop self-teaching modules for the oncology curriculum; to offer educational opportunities to enrich the private practitioners knowledge in the area of dental oncology; to provide and improve a biopsy service within the LSU School of Dentistry; and to develop a summative evaluation model.

Accomplishments: Through the support received from the clinical Cancer Education Grant we have been able to provide improved oral care to cancer patients at Charity Hospital. Through the efforts of the individuals involved in our Cancer Education Program we have also been able to provide our students with the knowledge necessary so that they can treat many of the dental problems encountered in cancer patients in their own communities. The course on oral oncology has been improved to increase the amount of time spent on the topics of epidemiology and chemotherapy to reflect the needs as evidenced by the workload which we have experienced in a hospital setting. Student contact with cancer patients has been increased through the activities of the community and preventive dentistry department in conjunction with the Department of Otolaryngology of the LSU School of Medicine. There has been an increase in the number of patients available in the clinic at the time that the students rotate through the hospital. The Summer oncology Fellowships increased the amount of time students spend in actual contact with patients. During these Summer Fellowships we have been able to intensify the participation of undergraduate dental students in actively treating cancer patients.

With the cooperation of the personnel in the library here at the LSU School of Dentistry we have been able to identify and make available to students core material dealing with cancer. We are presently in the process of developing self-teaching modules to augment the material which is available in our core audiovisual file. During this past year several of our faculty members have participated in continuing education courses for practitioners in various parts of the state. Some of these activities have been sponsored by the American Cancer Society. Material developed through the Cancer Education Grant has been used during these courses.

During this past year the biopsy service here at LSU School of Dentistry has received intensive study. As a result of the study by the Cancer Educ-

Program Director: Margaret H. Edwards, M.D.

ation Committee, proposals are now before our clinical committee and our curriculum committee to provide transfer of responsibility for the administration of the biopsy service from the Department of Community and Preventive Dentistry to the Department of Oral Diagnosis.

Along with other changes which have been made in the administrative structure of this program it should lead to a better coordinated effort to assure that all students participate and perform biopsies. We have developed a summative evaluation test. This test has now been used two times. The test continues to be modified and reviewed by a special subcommittee of our Clinical Cancer Education Committee. When the test is completed it should provide a means of measuring the cancer education program here at LSU School of Dentistry.

Plans: We will continue to expand our core references material by the addition of other self-teaching modules. Work will continue on the cancer education test to assure its reliability and to make certain that it reflects the cancer education effort here at LSU School of Dentistry. With the changes made in the biopsy service we hope that this will improve the educational opportunity for undergraduate dental students in this area. The Clinical Cancer Education Committee will closely monitor this effort and make any changes necessary.

It is the intention of the Clinical Cancer Education Committee to expand our Summer Oncology Fellowship program. We hope to do this by expanding the number of institutions to which our students will be able to go for these Fellowships. During the year we will be in contact with various institutions throughout the country to make arrangements so that this is possible. The Clinical Cancer Education Committee will continue to seek new approaches and new involvement of our students in the treatment of cancer patients, particularly in the areas of radiation therapy and chemotherapy.

From 07/01/76 to 06/30/84 FY 81: \$ \$70,271

Dr. John Beumer, UCLA School of Dentistry
10833 Le Conte Avenue, Los Angeles, CA 90024Objectives:

1. For undergraduate students and dental hygiene students:
 - a. Expand the learning experience in the basic concepts of oncology and in particular, oral and head-and-neck cancer.
 - b. Provide opportunities via clinical exposure for students to develop and sharpen their skills in cancer detection and diagnosis.
 - c. To expose students to the principles of cancer care and to provide opportunities to observe the clinical results of therapy.
 - d. To provide didactic instruction supplemented with clinical exposure in the dental and oral care of patients treated for head-and-neck cancer.
2. For postdoctoral dental students and dental residents:
 - a. To expand in detail all students/residents' basic knowledge and understanding of neoplastic disease with particular emphasis on head-and-neck cancer, including cancer biology, epidemiology, cancer management, including prevention, diagnosis, treatment, rehabilitation and oral health maintenance.
 - b. To provide prosthodontic postdoctoral students and second year General Practice Residents didactic and clinical instruction in the dental care and rehabilitation of patients treated for head-and-neck cancer.
 - c. To provide appropriate opportunities for dental and dental hygiene practitioners to update their knowledge in oral cancer detection, treatment and rehabilitation.

Accomplishments:

1. Predoctoral Program:

Funding has allowed development of a one-week block on cancer for all senior dental students (95-100 per year) and dental hygiene students (46-48 per year). The block utilizes seminar and didactic course work in combination with clinical exposure to cancer patients. During the past year approximately 100 biopsies were taken by block students, 60 surgical resections observed, 120 patients seen during head-and-neck tumor conferences and about 150 patients seen in various stages of rehabilitation. Comparisons of pre-test and post-test recovery indicates substantial improvement in knowledge of cancer which we feel is primarily due to the fact that didactic material can be demonstrated via clinical exposure during the block. The block consumes 45 hours of faculty-student exposure time per week.
2. Postdoctoral Program:
 - a. Two Clinical associates have been trained in Maxillofacial Rehabilitation.

Program Director: Margaret H. Edwards, M.D.

Both are seeking academic careers in institutional settings. One is at the University of Michigan and the other at the University of Vancouver.

- b. Ten postdoctoral students in prosthodontics have been trained so as to provide some rehabilitative dental and oral care for patients treated for head-and-neck cancer.

3. Continuing Education:

Numerous (7) courses and presentations have been given to practicing dentists and dental hygienists. Approximately 600 practitioners have attended these presentations, most from the southern California area.

Plans:

- 1. Continue the one-week cancer rotations for predoctoral dental students and dental hygienists.
- 2. Continue the clinical associate program in Maxillofacial Prosthetics.
- 3. Update the clinical experience for postdoctoral students.
- 4. Continue present activities in continuing education.

Grant 18748: Immunochemical Studies of Prostatic Acid Phosphatase

From 09/01/75 to 08/31/81

FY 81: \$0 (Ann. \$60,738)

Dr. Byung-Kil Choe, Department of Immunology and Microbiology, Wayne State University, School of Medicine, 540 E. Canfield Avenue, Detroit, Michigan 48202

Objectives: One of the antigenic markers for prostatic carcinoma, prostatic acid phosphatase (PAP), has been evaluated last few years for its usefulness in staging the disease. The objectives of our study was to characterize PAP antigenically and structurally through the cleavage and sequencing of antigenic polypeptides derived from the purified enzyme and through the comparative study of PAP with lysosomal acid phosphatase. Furthermore, additional prostate specific antigens have been searched in the human prostatic tissue in order to develop immunological assay methods for these presumptive tumor markers. Those immunochemical studies of prostatic cancer marker antigens are expected to serve as valuable adjuncts in the staging of the disease.

Accomplishments: In efforts to define the antigenic specificity of the PAP, detailed structural analyses have been initiated involving fragmentation of the enzyme; a functional domain of the enzyme was identified by the CNBr cleavage and a limited proteolysis. A fragment of enzyme which corresponds to approximately 1/5 of the subunit exhibited catalytic activity after the interaction with specific antibodies. This region seems to define the active site domain. Monoclonal antibodies to PAP have been obtained by the Kohler-Milstein's hybridoma technique. Preliminary antigenic mapping studies of PAP in comparison with lysosomal acid phosphatase preparation indicated that there are a few antigenic domains specific to PAP molecules.

We have elaborated a double antibody immunoenzyme assay (IEA) which is simpler, more economical and theoretically more reliable than a radioimmunoassay (RIA). In order to define the role of IEA and RIA in the detection and staging of prostatic carcinoma, a large number of serum samples were assayed. All of the clinically staged B patients with positive IEA-PAP were shown to have metastasis after surgical staging.

In search of additional prostate marker antigens we have analyzed non-PAP proteins from prostate extracts. Thus far, proteins of molecular weights 60,000, 33,000 and 13,000 are identified as candidates.

Plans: The role of prostatic acid phosphatase (PAP) immunological assays will be evaluated for the detection and staging of prostatic carcinoma. Using radioimmunoassay, immunoenzyme assay and immunohistological methods, the frequency of lymph node metastasis in early-stage carcinoma will be investigated by immunoassays with a large number of patients. Antigenic structure of PAP will be investigated by the uses of monoclonal antibodies and techniques of peptide analysis in order to define the antigenic determinants in terms of peptide structure. Lysosomal acid phosphatase will be also purified and be compared with PAP for their antigenic and peptide structure. Additional prostate specific marker antigens will be also purified and characterized in order to use them in the clinical correlative studies.

Program Director: Andrew Chiarodo, Ph.D.

Publications:

Frost, P., Rose, N.R., Choe, B.K., and Pontes, E.J. Immunology of Prostate Cancer, Chap. 17, In: Accessory Sex Glands of the Male Reproductive Tract, E. Spring-Mills and E.S.E. Hafez (Eds.) Elsevier/North Holland, Inc., New York. pp. 311-326, 1980.

Choe, B.K., Rose, N.R., Pontes, E.J. Radioimmunoassay for Human Prostatic Acid Phosphatase, In: Prostatic Carcinoma. E.S.E. Hafez and E. Spring-Mills (Eds.), Martinus Nijhoff BV Publishers, Hague, Netherlands. pp. 131-140. 1980.

Choe, B.K., Pontes, E.J. and Rose, N.R. Methods for the Detection of Human Prostatic Acid Phosphatase, In: Manual of Clinical Immunology. Rose, N.R. and Friedman, H. (Eds.) American Society for Microbiologist, Washington, D.C. pp. 951-962, 1980.

Choe, B.K., Pontes, E.J., Dong, M.K. and Rose, N.R. Double-antibody Immunoenzyme Assay for Human Prostatic Acid Phosphatase. Clin. Chem. 26:1854-1859, 1980.

Choe, B.K., Dong, M.K., Walz, D. and Rose, N.R. Antibody Restores Catalytic Activity of a Small Molecular Weight Fragment of Human Prostatic Acid Phosphatase. Molecular Immunol. Vol. 18 (In Press). 1981.

Choe, B.K. and Rose, N.R.: Chapter 17, Prostatic Acid Phosphatase, A Marker for Human Prostatic Adenocarcinoma. In: Methods in Cancer Research, Vol. 19, Busch, H. and Yeoman, L.C. (Eds.) Academic Press, New York, (In Press). 1981.

Rose, N.R., Choe, B.K. and Pontes, E.J. Chapter 14, Prostatic Acid Phosphatase. In: Prostatic Cancer, Ablin R. (Ed.) Marcel Dekker Inc., New York. (In Press). 1981.

Choe, B.K., Pontes, E.J., Lillehoj, H.S. and Rose, N.R. Immunohistological Approaches to Human Prostatic Epithelial Cells. The Prostate, 1:383-398. 1980.

Grant 18863: Monitoring Familial Medullary Carcinoma of the Thyroid (Yale)

From 06/01/76 to 05/31/81 FY 81: 0 (Ann. \$80,399)
Dr. M. Genel, Yale University, 333 Cedar Street, New Haven,
Connecticut 06510

Objectives: This program was devised to establish an effective procedure to detect clinically unrecognized medullary carcinoma of the thyroid, pheochromocytoma, and other manifestations of the familial syndrome of multiple endocrine neoplasia type II. As an autosomal dominant trait a 50% incidence of malignancy is anticipated in family members at risk. The program design provides convenient screening to members of a large New Haven kindred comprising more than 140 members, over a third of whom are under 20 years of age. The program emphasizes utilization of paramedical personnel with minimal inconvenience and minimal risk to the subjects being screened.

Accomplishments: A procedure utilizing 3 family "spokesmen" with whom contact with family members is initiated and maintained was devised and has succeeded in soliciting cooperation of over 2/3 of the members of the family within their geographical area. Meetings with these family spokesmen have been held annually. At these meetings progress of the program is reviewed, problems encountered are discussed and where possible procedures altered accordingly. At the beginning of 1980 our screening procedure was changed to use a combination of a short calcium infusion and pentagastrin. This combination has been reported to be more effective than pentagastrin alone in eliciting a calcitonin response from subjects with medullary carcinoma or its precursor, C-cell hyperplasia. Using this more sensitive technique an abnormal calcitonin response was found in a 10 year old boy who had been previously negative on testing. Total thyroidectomy was performed and histology confirmed the presence of medullary carcinoma of the thyroid. Screening of other members of the family continues and positive calcitonin responses have been found in two further persons who have had total thyroidectomies in the past. They are being investigated for possible local recurrence or distant metastasis. Three members of a second family with the same trait have been screened using the same procedure. In a 33 year old woman who has previously had a thyroidectomy for medullary carcinoma, high urinary catecholamine levels were discovered. It is anticipated that she will have surgery for pheochromocytoma in the near future. Her children have been negative on screening. Intensive efforts to gain information on genetic linkage between the trait for familial medullary carcinoma and easily identifiable red and white cell antigens have been initiated. It is hoped that these studies will enable us to define more accurately which members of the family are truly at risk and which need no longer be screened.

Plans: The period of the grant as originally funded expires on 5/31/81. We have applied for an extension of this period to use hitherto unexpended funds and intend to submit a new grant for a July 1, 1981 deadline. The new grant would emphasize our studies of genetic linkage. Such studies, if successful, could more clearly delineate the at risk population, permit consideration of prophylactic thyroidectomy in certain very high risk individuals, and provide invaluable basic information on the biochemical nature of the trait which predisposes to familial endocrine neoplasia type II.

Program Director: Richard D. Costlow, Ph.D.

Grant 18901: Evaluation of Rehabilitation of Oropharyngeal Cancer

From 09/01/75 to 08/31/81

FY 81: 0 (Ann. \$74,610)

Dr. Jerilyn A. Logemann, Northwestern University Medical Center, Chicago, Illinois 60611

Objectives: This project is designed to define and quantify changes in speech and swallowing resulting from treatment for oral cancer, to assess the psychosocial effects of treatment on the patient and his family, and to utilize this information in designing and evaluating rehabilitation programs to re-establish normal communication and deglutition. It is the overall goal of this research to improve patient functional outcomes after treatment for oral cancer by applying data on functional changes after treatment and on specific rehabilitation procedures to the design of optimal rehabilitation protocols.

Accomplishments: During this year, speech and swallowing measures of oral cancer patients have been made pre-treatment, post-treatment at time of reinitiation of oral feeding, at one month, three months and six months later. In addition, three questionnaires have been given to patients pre-treatment, monthly for three months post-treatment, then every three months for one year. The questionnaires gather information on the patients' frequency and nature of communication, eating, and socialization procedures. Results of the functional studies indicate that patients with the same surgical resection and reconstruction show essentially identical functional changes. There is minimal inter- and intra-subject variability on the speech and swallowing measures when patients are carefully categorized according to the extent and nature of the ablative and reconstructive procedures. When functional changes in speech and swallowing were compared across groups it was clear that each group has a distinct profile of functioning, different in the detailed characteristics of swallowing motility and speech articulation. It was also apparent that the severity of speech and swallowing dysfunction after surgery relates to the extent of the lingual resection and the nature of the oral reconstruction, with nature of the reconstruction the most important predictor of function in patients with less than one-half of the tongue included in the resection. Diet and eating patterns of the patients in this study were examined by questionnaire and a profile of diet performance generated. Comparison of diet profiles and data on swallowing function indicate that when combined oral and pharyngeal transit times are greater than 10 seconds for a particular material, patients eliminate that food consistency from their diet. Results of the eating questionnaire indicate that 72% of the patients eliminated eating as a social behavior. For all patients included in the study eating was an occasion for socialization outside the family at least once per week prior to treatment. After treatment, 75% of the patients ceased this socialization and did not resume it within the first year after treatment.

Plans: Results of these studies provide detailed information on the many changes in eating, talking and socialization faced by specific groups of treated oral cancer patients. Plans are to apply this information to the development and evaluation of several such new and potentially more effective speech/prosthetic and nutritional rehabilitation techniques.

Program Director: Lawrence D. Burke

Publications:

Logemann, J.A., Sisson, G.A., and Wheeler, R.: The team approach to rehabilitation of surgically treated oral cancer patients. Proc. Nat'l Forum Cancer Rehab., pp. 222-227, 1980

Georgian, D., Logemann, J., and Fisher, H.: Compensatory articulation patterns of a surgically treated oral cancer patient (IN PRESS)

From 01/07/76 to 06/30/84

FY 81: \$95,926

Dr. Pedro J. Santiago-Borrero, University of Puerto Rico School of
Medicine, G.P.O. Box 5067, San Juan, Puerto Rico 00936

Objectives: This program has been conceived in such a way as to offer the undergraduate medical student the opportunity to familiarize himself in an integral form with the methodology used in the diagnosing of neoplastic disease, to help the student develop the necessary skills and know-how which would enable him to understand the basic principles involved in the management of cancer. At the graduate level the physician will have acquired the necessary knowledge and skills to enable him to understand fully and to discuss the most fundamental aspects of the epidemiology, pathology, clinical aspects, diagnosis, prevention of cancer and the indication and contra-indications of the various forms of therapy.

Accomplishments: (1) Specialized Cancer Clinics (Surgery Tumor Clinic, Head and Neck, Breast, Radiotherapy, Adult Chemotherapy and Children Solid Tumors and Chemotherapy Clinics). During the period covered by this report 286 of these clinics were conducted with the participation 1,104 physicians and students and the presentation of 11,648 patients. (2) Treatment Planning Conferences. Three T.P.C.'s have been organized: one devoted to Surgery and Subspecialties, a second devoted to Hematology and Radiotherapy and a third to Gynecology and Pediatrics. These activities have succeeded in obtaining full participation of all clinical departments. Excluding the cancers of skin, over 90% of all cancer patients of the institution were presented to these activities. (3) Cancer Journal Club - It is held once a week with the participation members of the departments of Surgery, Gynecology, Radiotherapy, Pediatrics, Pathology, Oral Surgery and the Sections of Urology and E.N.T. (4) Cancer Seminars and Cancer Conferences. These have been conducted with the participation of local and outside visiting lecturers. Nine of these activities were held during the period covered by this report. (5) Basic Course in Cancer. This course is conducted during the month of February every year with the cooperation of about 30 lecturers from the departments of Medicine, Surgery, Pathology, Biochemistry, Pharmacology, Microbiology and Radiotherapy. This course is aimed at acquainting the student in depth with the present state of the science of cancer biology and recent clinical advances. (6) Summer Cancer Course. This course is also conducted once a year during the months of June and July and is aimed at acquainting the clinical assistants in depth with the present state of the science of cancer biology and recent clinical advances. (7) Cancer Grand Rounds. These are conducted separately on a weekly basis in each principal department by their respective cancer services.

Plans: (1) to continue all teaching activities described in above paragraph; (2) to supervise and improve the cancer core curriculum at undergraduate level; (3) to extend teaching activities to a medical consortium organized around the island by the School of Medicine in cooperation with the Department of Health; (4) to expand and promote most of the teaching activities to make them accessible to community physicians through continuous medical education programs and (5) to help and stimulate other hospitals to establish Cancer Education Programs.

Program Director: Margaret H. Edwards, M.D.

Grant CA 18940: A Tumor Control Center Program

From: 06/30/76 - 05/31/81 FY 81: 0 (Ann. \$162,304)
Dr. Leslie Whitney, P.O. Box 1668, Wilmington, Delaware 19899

Objectives: To continue to expand and improve the Cancer Control Program of the Delaware Cancer Network, a voluntary agency with the following formal affiliates: all seven non-governmental hospitals in the State; the Delaware Division of the American Cancer Society; the University of Delaware, the Medical Society of Delaware, the Visiting Nurse Association of Wilmington, Inc., and the Division of Public Health of the State of Delaware, Department of Health and Social Services. Over the history of this Grant, emphasis has been placed on the development of locally coordinated cancer control programs at each of the Network affiliates. The overall objective of the program has been to insure that high level quality cancer care services are available to each Delaware citizen in a facility as close to the patient's home as possible.

Accomplishments: (1) Affiliation agreement with all non-governmental hospitals, Visiting Nurse Association, University of Delaware, and Delaware Division, American Cancer Society; (2) Identified, appointed and indoctrinated, and continued to work with the Cancer Coordinator in each affiliated hospital as recommended by the hospital medical staff; (3) Employed competent professional staff in Nutritional Services, Health Education, Nursing Education, Social Services, Evaluation Planning and Data Retrieval and Analysis. Accomplished goals specific to each element of program; (4) Promoted planning, application, and consultation to all hospitals for new or continuing certification by American College of Surgeons Commission on Cancer; (5) Provided technical assistance to all areas of professional education, working closely with American Cancer Society and Cancer Clinic staff for transfer of technology; (6) Transferred the planning, maintenance and management of Tumor Clinics to the supporting hospitals; and (7) Conducted a "Pain Management for Cancer Patients" Regional conference, evaluated the program and disseminated the results.

Plans: Program Terminated on 05/31/81.

Publications: Wingate, B., et al: Opening New Doors, A Resource Guide for Cancer Patients Living in Delaware, Wilmington, DE
The Wilmington Medical Center, Delaware Cancer Network, May 1980.

Program Director: Margaret E. Holmes, Ph.D.

From 07/01/76 to 06/30/84 FY 81: \$87,055
Dr. John F. Potter, Georgetown University Medical School
3800 Reservoir Road, M.W., Washington, D.C. 20007

Objectives: The Clinical Cancer Education Program is designed to improve education and training in oncology within and external to the University for medical students, residents, clinical associates, post-graduates at diverse levels, and other medical and health care professionals. This mission shall be attained through: (1) qualitative and quantitative improvements in oncology education for sophomore medical students; (2) systematic analysis and evaluation of the oncology course; (3) expansion of multidisciplinary cancer education programs and conferences so as to enhance the continuing education of trainees and practitioners; (4) development of a effective information resources program to augment the overall cancer teaching program; (5) support of clinical assistants (undergraduates) during the summer for participation in specific Center research programs; (6) training of clinical associates in the oncologic specialties.

Accomplishments: (1) Curricular design and direction of an oncology course for sophomore medical students consisting of 13 hours in carcinogenesis, radiation medicine, gastrointestinal neoplasia, gynecologic neoplasia, breast cancer and Wilm's tumor as well as 3 hours in the pharmacology of chemotherapeutic agents. (2) Training of four clinical associates - three in medical oncology and one in pediatric oncology. (3) Support and teaching of ten clinical assistants at various stages of their medical education in the areas of clinical research (radiation medicine, medical oncology, pediatric oncology, and pharmacology) as well as basic laboratory research (immunologic oncology). (4) Improved operation of the clinical cancer information program and maintenance of core oncology reference files for the Center's clinical divisions. (5) Planning and direction of several post-graduate educational programs including symposia, specialty tumor boards and multidisciplinary cancer conferences aimed at broadening the scope of the Center's educational activities - an international symposium on the "Management of Patients with Terminal Cancer", a major conference on "Steroid Hormone Receptors in Primary and Metastatic Carcinoma of the Breast" and weekly conferences relating to cancer prevention, detection, diagnosis, treatment and rehabilitation. (6) Establishment and refinement of systematic evaluation of the total cancer program.

Plans: The future plans for the Clinical Cancer Education Program include expansion of the curriculum for the sophomore oncology course; direction of and international symposium on "Prostaglandins and Cancer" as well as other multidisciplinary conferences targeted for students, trainees and practitioners; training of clinical associates and clinical assistants with a special emphasis in academic medicine and research; and expanded efforts in evaluation and needs assessment to augment the future design of the program.

Program Director: Margaret H. Edwards, M.D.

Grant 19087: Clinical Cancer Education Program

From 07/01/76 to 06/30/84 FY 81: \$78,891
Dr. John Mendelsohn, University of California, San Diego,
School of Medicine, La Jolla, California 92093

Objectives: This interdisciplinary training program is designed to provide medical students and physicians with training in oncology, covering clinical practice as well as aspects of biology and biochemistry relevant to the cause, pathophysiology, treatment and prevention of cancer. The clinical oncology divisions of the Departments of Medicine, Surgery, Pediatrics, Radiology and Reproductive Medicine have established an interdisciplinary training program for Clinical Associates which is supported by this Clinical Cancer Education Grant. Clinical Assistants (medical students) are supported to pursue research interests in depth under the close supervision of a faculty member. Continued emphasis on the planning and evaluation of clinical trials through clinical experience and teaching conferences continues to be an objective of this program.

Accomplishments: Seventeen clinical associates and 12 clinical Assistants have been supported on this clinical Cancer Education Grant. An oncology concentration area has been developed for medical students. New clinical teaching conferences for students and physician trainees have been developed, with a strong emphasis on the planning and evaluation of clinical trials. Within the past year, inpatient oncology services have been established at both the University Hospital and the Veteran's Administration Medical Center. Clinical associates are involved in teaching and monitoring all protocol and nonprotocol-based oncologic evaluation and therapy in the inpatient and out patient units at both facilities. The logic of protocol regimens and ensuing practical interdisciplinary relationships are routine exposure for all trainees. Clinical associates are also active in consulting roles outside the special oncology units at both facilities. Teaching conferences and multidisciplinary tumor boards with both faculty and clinical associates participating are held weekly. Topics include protocol activities, clinical reviews of specific disease areas or analyses of controversial therapeutic alternatives stimulated by patients seen in consultation or on the inpatient units. A twice-monthly afternoon teaching session examines important issues in cancer. Evaluation of clinical associates is done annually. Clinical associates evaluate the educational program, as well as the faculty members who participate in their training. Clinical assistants submit evaluations of the research projects which they conducted during the summer. Evaluations by all the faculty sponsors are also submitted.

Plans: Recent budget cuts have reduced our clinical associates to 31 for next year. The summer research projects for medical students (clinical assistants) will not be continued. Faculty will continue to participate in the Human Disease undergraduate lecture series. Teaching conferences will be continued, and a complementary series of sessions in clinical cancer pharmacology is being developed for the next academic year. Clinical associate training will continue to include inpatient/outpatient unit experience as well as protocol studies.

Program Director : Margaret H. Edwards, M.D.

From: 06/30/76 to 11/30/82

FY 81: -0- (Ann. \$60,705)

Dr. Henry W. Strobel, The University of Texas Health Science Center, Houston
Medical School, P.O. Box 30708, Houston, TX 77025

Objectives: To define: 1) the role of the colonic microsomal drug metabolism system in both carcinogenesis and chemotherapy; 2) the factors which regulate its activity; and 3) the mechanism(s) of colon carcinogenesis involving bioactivation. Knowledge of how the bioactivation of carcinogens takes place in the colon and knowledge of how this activation is regulated will enable us to develop appropriate interventions.

Accomplishments: We have demonstrated for the first time that the colon has an active, inducible drug metabolism system capable of activating drugs and carcinogens. We have shown that the colon mucosal drug metabolism system is responsive to gastrointestinal (GI) hormones. We have observed dramatic responses (2- to 4-fold induction) in certain colonic hydroxylation activities after treatment with pentagastrin, secretin, and cholecystokinin octapeptide. These increases are apparently due to the synthesis of new enzymes since the induction is prevented by simultaneous injection of cycloheximide, an inhibitor of protein synthesis. Thus the activation of drugs and carcinogens appears to be under the regulatory control of the GI hormones, though there are doubtless other levels of control yet to be identified. Nonetheless, fluctuations in the level of GI hormones normally induced by dietary composition affects colonic drug metabolism activity levels and consequently the metabolites produced.

Another major accomplishment lies in the development of a human colon tumor cell line as a system for the study of drug metabolism. We have shown that this human adenocarcinoma has high basal levels of cytochrome P-450 and responds dramatically to induction. A significant consequence of the use of the human cell line in culture is the demonstration that human colon tumors will activate cyclophosphamide to its hydroxylated cytotoxic metabolite and that the hydroxylated metabolite will kill colon adenocarcinoma cells quite effectively. Furthermore, the activation and cytotoxicity is inducible by denzanthrane pretreatment. Thus we have been able to show a positive effect of cyclophosphamide treatment of colon tumor cells in culture, raising the possibility again for the use of this agent in patients.

Plans: We will continue our efforts to define the mechanisms and consequences of inducing colonic drug metabolism activities by GI hormones. We will determine which cytochromes P-450 are specifically increased by GI hormone pretreatment and the effects of this induction on alteration in metabolites of carcinogenic substrates. We will also focus efforts on development of the human colon tumor cell model and define the ability of GI hormones and other inducers to regulate these processes.

Publication: Fang, W.F., and Strobel, H.W.: Control by Gastrointestinal Hormones of the Hydroxylation of the Carcinogen benzo[*a*]pyrene and Other Xenobiotics in the Rat Colon. Cancer Res., 41:1407-1412, 1981.

Program Director: Vincent J. Cairoli, Ph.D.

Grant 19134: Cancer Care Data Management System

From 10/31/77 to 12/31/81 FY 81: \$150,984 (estimated)
Dr. Robert H. Friedman, University Hospital, 75 E. Newton Street
Boston, Massachusetts 02118

Objectives: The primary objective is to design a computerized data management system which overcomes traditional medical record deficiencies in an ambulatory medical oncology setting. Specific goals are: (a) to support patient care and clinical research data collection within a single system; (b) to customize data entry and display routines on the basis of diagnosis and treatment; (c) to monitor data as it is entered into the computer, and alert staff to potential data and medical problems; (d) to make essential cancer care information immediately available to clinicians via direct communication with the computer. The proposed system should be cost-effective and transferable to other cancer care sites.

Accomplishments: After a 3-month pre-test of the system involving 20 patients, major components of the CDMS were implemented for the entire medical oncology clinic population of 160 active cases in July 1979.

The system produces a computer-generated medical record. Included are reports which cover demographic information, general and oncologic history data, patient management-oriented flowsheets, data summaries, and hospital reports. Interval (visit) information is collected on computer-generated turnaround forms (Encounter Forms), which are customized for each patient based on cancer site, therapy, and individual case characteristics. A Chemotherapy Treatment Decision Form is also generated for each patient which assesses treatment eligibility based on the data on file for the patient and rules on file for his treatment regimen. Before parenteral therapy is given in clinic, proposed drug doses are checked by an interactive program for potential dosage errors. During the clinic visit, the computer prints a check-off order form which lists tests and procedures needed, and "due dates" for each. A series of statistical programs are also available which enable users to subset the patient population, compile M x N and actuarial life tables, perform correlation and a scattergram analyses and analyses of variance, and run single-variable description statistics on any variable stored in the database.

The CDMS is programmed in SM-11 standard MUMPS and is supported in its current application by an on-site PDP 11-34 computer. Computer terminals (both video and printer) have been installed in key areas throughout the institution to provide staff with immediate access to patient data. In addition, special reports are regularly generated which alert the staff to abnormal laboratory results and outstanding laboratory and medical record information.

The system's appointment-logging function supports patient scheduling in the clinic. An Extended Patient Registry provides summary data for the entire population, and has proved useful for administrative and research purposes. An accounting system which tracks users through their interactions with the system has been in operation since October 1979 and has demonstrated a significant level of discretionary use by the clinical staff. Preliminary evaluation studies

Program Director: Donald N. Buell, M.D.

conducted after six months of implementation indicate that the CDMS has had a positive impact on data quality and completeness. Plans are underway to transfer the CDMS to several other institutions involved in cancer care.

Plans: During the third year of the current project, procedures will be developed which use the CDMS to execute protocol rules with regard to baseline data collection, test ordering, and complex dose modifications.

Additional administrative supports will also be developed during this period, and work will begin on the development of a set of statistical programs for the analysis of research data and accumulated clinical experience. Evaluation studies will continue to measure the impact of the CDMS on patient care and clinical research.

Publications:

Friedman, R.H., Horwitz, J., Concannon, T., Krikorian, J.G., and Lopez, J.A.: Decision-Making Support for Patient Care and Clinical Research Within Cancer Information Systems. Proc. Third Annual World Association of Medical Informatics, 1980.

Friedman, R.H., Horwitz, J.H., Concannon, T.C., and Krikorian, J.G. An Information System for Clinical Management in Oncology. Proc. 1980 MUMPS Users' Group Meeting. San Diego, 1980

Friedman, R.H., Krikorian, J.G., Horwitz, J.H., and Concannon, T.C. An Information System for Clinical Research: The Cancer Data Management System. MEDINFO 80, Tokyo 1980.

Friedman, R.H., and Horwitz, J.H. Issues in Automation of Cancer Treatment Protocols. Proc. Fourth Symposium on Computer Applications in Medical Care, Washington, D.C. 1980.

Horwitz, J.H., Gertman, P.M., Thompson, H., Friedman, R.H., Concannon, T.C., Kreger, B.E., Krikorian, J.G., Lopez, J., and Bedford, J.E. Computer-Assisted Patient Care Management in Medical Oncology. Proc. Fourth Symposium on Computer Applications in Medical Care. Washington, D.C. 1980.

Conrad, L., Bloom, S., Cooper, C., Concannon, T., Friedman, R.H., Horwitz, J.H., Krikorian, J.G., and Lopez, J., The Cancer Data Management System Statistics Package. Proc. Fourth Symposium on Computer Applications in Medical Care. Washington, D.C. 1980.

From: 02/01/76 to 01/31/82

FY 81: \$220,425

Dr. John E. Shively (formerly Dr. Charles W. Todd), City of Hope Research Institute, 1450 East Duarte Road, Duarte, CA 91010

Objectives: The major short term objectives of this research are to compare the primary protein and carbohydrate structures of carcinoembryonic antigens (CEA), including CEA, tumor extract (TEX), and normal cross-reacting (colon) antigen (NCA); to apply this knowledge to the development of specific immunoassays for each; and to initiate pilot clinical studies comparing the levels of these tumor markers in cancer patients. These studies will contribute to our understanding of these tumor markers at the molecular level, and should reveal the degree of relatedness and complexity of this family of genes. The pilot clinical studies will help to translate our basic science studies into the initial phases of clinical studies. The overall long-term objective is to gain an understanding of the progressive changes from normal to malignant in colonic epithelial cells. We intend to clone the CEA family of genes and to study their distribution, structure, and methylation patterns, in normal and malignant colonic tissue.

Accomplishments: CEA, TEX, and NCA have been isolated from a single tumor, treated with anhydrous hydrogen fluoride to remove all carbohydrate except for the N-acetyl-glucosamine attached to asparagine by an N-glycosidic bond, reduced and carboxy-methylated at cysteine residues, trypsinized, and the resulting peptides separated by reverse phase high performance liquid chromatography (HPLC). Although the amino acid compositions of all three antigens are closely similar they differ in that CEA has no methionine, but TEX and NCA have 4-5 residues per polypeptide chain, and, except for a few peptides in common, give very different tryptic maps on HPLC. Work is now in progress to sequence each tryptic fragment by our microsequencing methodology (1 nmole). Concurrently, we are attempting to clone cDNA corresponding to the mRNA of CEA. The cell line SW403, a high producer of CEA, has provided mRNA which has already been cloned into a cDNA library. Screening for relevant clones is now underway. Clinical screening of cancer patients (265) for the serum levels of CEA and TEX has been completed.

Plans: Long-range plans include the mapping of colonic antigens in normal, premalignant, and malignant tissue by the combined use of hybridoma antibodies and 2-d gels. Antigens which correlate with tumorigenesis will be structurally characterized by our microchemical methodology, and screened for in-patient sera by our established radioimmunoassay and ELISA techniques. The ultimate goals of cloning the cDNA for CEA are to study the genomic organization of the entire CEA family of genes.

Publications:

Shively, J.E. and Todd, C.W.: Carcinoembryonic Antigen A: Chemistry and Biology. In Cancer Markers: Developmental and Diagnostic Significance, S. Sell, Ed. Clifton, New Jersey, Humana Press, 1980; pp. 295-314.

Pompecki, R., Shively, J.E., and Todd, C.W.: Sensitive Detection of Carbohydrate Determinants on CEA Preparations by Lectin and Antibody Binding Using Polyethylene Glycol, *Cancer Res.*, in press.

Program Director: Vincent J. Cairoli, Ph.D.

From 09/01/75 to 08/31/82

FY 81: \$0 (Ann. \$76,549)

Dr. M.A. Bean, Virginia Mason Research Center, Seattle, Washington

Objectives: The continuing goal of our research program is to determine the role of cellular immune responses in the biology of bladder carcinoma. That is, does cellular immunity play a role in preventing the spread and metastasis of this tumor? We are continuing to focus on the question of whether or not bladder cancer patients have tumor-antigen induced suppressor (immunoregulatory) T-cells. If such cells exist in humans (as they do in rodent systems), then new approaches to treatment of bladder cancer through therapies aimed at abrogation of these immunoregulatory cells may be of value in the therapy of bladder cancer.

Accomplishments: For our studies we have been using the one-way mixed leukocyte culture (MLC) as a measure of cellular immune responsiveness in vitro. We have studied the effects of exposure of the patient's lymphocytes to his own tumor cells on the ability of the lymphocytes to mount a blastogenic response in MLC. With this assay we have observed three different patterns of response. The first of these is that of selective suppression. That is, when the patient's lymphocytes are exposed to his own tumor cells, the ability of the patient's lymphocytes to respond in MLC is decreased whereas the addition of the same tumor cells to lymphocytes from normal donors does not affect or augment their lymphocyte responsiveness. The second pattern is nonspecific suppression. That is, the addition of tumor cells depresses the ability of lymphocytes from both the patient and normals to respond in MLC. The third pattern is a lack of suppression of the lymphocyte responses of both the patient and the normals when exposed to the tumor cells. Of 19 bladder cancer patients, 13 exhibited selective suppression, 0 nonspecific, and 6 showed no suppression. Of 30 patients with other types of cancers, we observed selective suppression in 18, nonspecific suppression in 4, and no suppression in 8. Although additional studies are warranted, it would appear that we can detect and study tumor-triggered suppressor cells in this fashion.

Plans: For the coming year we plan to focus on two questions. The first of these is whether or not the presence of suppressor cells in the blood correlates with the stage and/or biologic activity of these patients' tumors. The second question is whether we can identify the suppressor T-cell that is being triggered by contact with tumor by using monoclonal antibodies reactive with subpopulations of T-cells.

Publications: Bean, M.A.: Cell-mediated Immune Reactions to Human Cancer Antigens and their Regulation. In Burchenal, J.H., and Oettgen, H.F. (Eds.): Cancer: Achievements, Challenges and Prospects for the 1980s. New York, Grune and Stratton. 1981. pp. 333-342.

Program Director: William E. Straile, Ph.D.

Grant 19171: Case-Control Study of Carcinoma of the Pancreas

From 04/01/76 to 03/31/81

FY 81: 0 (Ann. \$93,218)

Thomas M. Mack, M.D., University of Southern California, School of Medicine,
Los Angeles, California 90033

Objectives: This case-control study of pancreas carcinoma has been designed to test etiologic hypotheses, identify groups at high risk, and generate further etiologic hypotheses by the simultaneous analysis of multiple environmental exposures and putative risk factors. Cases are identified through the LAC/USC Cancer Surveillance Program, and classified with respect to means of diagnosis. Controls matched for age, race, and sex are chosen from the neighborhoods of residence by a specific algorithm, and cases and controls are interviewed in their homes using a standard instrument covering occupational and avocational exposures, medical history and treatment, and habituations such as diet, smoking, and beverage consumption. Proxy interviews are done when the patient cannot be interviewed prior to death. Standard matched pair analysis will be performed, with separate analysis on subjects based on sub-site, conclusiveness of diagnosis, and method of interview.

Accomplishments: Interviews have been completed on 485 matched pairs, with about 30 additional pairs to be completed by interview of controls. Telephone interviews to obtain further information on certain items from approximately 40 selected cases and controls are also under way. Interview questionnaires are going through the final processes of coding and editing.

Plans: Analysis of data from this study will commence momentarily, with initial attention given to those items previously suggested to be risk factors, such as antecedent diabetes and pancreatitis and habitual smoking and coffee drinking, and those experiences newly found to be associated with the disease. The analyses should be complete by summer.

Publications:

Mack, T.M. and Paganini Hill, A.: Epidemiology of Pancreas in Los Angeles. Cancer 47: 1474-1483, 1981.

Program Director: William E. Straile, Ph.D.

Grant 19177: Carcinogenesis of Pancreatic Ductal Tissue In Vitro

From 04/01/79 to 03/31/82

FY 81: \$68,828

Sherwood Githens, Ph.D., Department of Biological Sciences, University of New Orleans, New Orleans, Louisiana 70122

Objectives: The goal of this project is to determine whether isolated and cultured pancreatic ducts can be used for the study of carcinogenesis in vitro. The rationale for this approach is that human pancreatic cancer usually is duct-like in morphology, suggesting that the disease originates in duct tissue. Pancreatic ducts of the hamster and rat have been used because pancreatic cancer resembling the human disease has been induced in those animals. Once convincing morphological evidence of enoplastic transformation of the cultured duct fragments is obtained, biochemical and immunological studies will be directed toward the identification of specific markers of the neoplastic process.

Accomplishments: Hamster pancreatic ducts in culture have been exposed to N-nitroso-bis(2-oxopropyl)amine (BOP) once at the beginning of the culture period or on a twice-weekly schedule. A dose of 0.1 ug/ml twice weekly produced the largest number of morphological lesions without frank toxicity over an eight-week culture period. Present efforts to enhance the presently undramatic effects of BOP include prior injection of the animals with betanaphthoflavon which may enhance the BOP-metabolizing capacity of the isolated ducts, inclusion of epidermal growth factor in the culture medium to enhance cell division, and addition of the tumor promoter TPA to the culture medium. Some ducts are being cultured for longer than eight weeks to determine whether neoplastic lesions simply need more time to develop. In addition to routine light and electron microscopic examination of the ducts, effects of BOP on DNA synthesis are being assessed by autoradiography. Because isolated and cultured ducts may have lost their capacity to respond to BOP, hamsters have been injected with doses of BOP known to result in a large incidence of pancreatic cancer in vivo. Ducts have been isolated from these pancreases one week after BOP injection and are being followed in culture. Because of the suggestion that islets may be the tissue of origin of hamster pancreatic cancer, experiments involving islets have been conducted in parallel with those described above. No effects of BOP on cultured islets have been observed thus far. Preliminary efforts are underway to apply the experience gained with the rodent pancreas to the isolation and culture of primate pancreatic ducts in order to develop the capability for similar studies of the human pancreas. A histochemical study of alkaline phosphatase and adenosine triphosphatase in the rat, hamster, and baboon pancreas has supported previous studies that show that these enzymes are not suitable markers for duct epithelium in most species.

Plans: Once convincing morphological evidence for early neoplastic changes in rodent ducts (and, ideally, human ducts) have been obtained, treated ducts will be injected into nude mice to confirm that the ducts are indeed neoplastic. Altered and normal ducts will be compared biochemically, by appropriate enzyme assays and by two-dimensional gel electrophoresis, and immunologically in order to identify specific markers associated with neoplastic transformation.

Program Director: William E. Straile, Ph.D.

Publications:

Githens, S. III, Holmquist, D.R.G., Whelan, J.F. and Ruby, J.R.:
Morphological and biochemical characteristics of isolated and cultured
pancreatic ducts. Cancer, 47:1505-1512, 1981.

Grant 19182: Pancreatic Carcinoma in Continuous Culture

From 09/01/76 to 08/31/82

FY 81: 0 (Ann. \$80,294)

Adel A. Yunis, M.D., University of Miami, Post Office Box 016960, Miami,
Florida 33101

Objectives: Carcinoma of the pancreas is the fourth killer cancer in the United States. Diagnosis is often not possible until the disease is relatively advanced and survival is short. None of the chemotherapeutic modalities have significantly altered the course of the disease. Our success in establishing human pancreatic carcinoma in continuous culture (MIA PaCa-2) six years ago has allowed us to use this cell line as an experimental model to study certain biological aspects which would hopefully be applicable to the clinical disease. These are: (1) the identification of tumor-associated antigens for use as markers for early diagnosis; (2) the exploration of various chemotherapeutic agents; (3) the investigation of the secretion of proteolytic activity by the cultured cells and its significance.

Accomplishments:

1. Tumor-Associated Antigen. We have previously described the identification of a pancreatic tumor associated antigen and the preparation of a highly specific antibody.

Using the highly sensitive immunoperoxidase reaction with human embryonic pancreas and adult pancreatic cancer tissue, the antiserum detected the pancreatic antigen in the intralobular and interlobular ductal epithelial cells of the tissue.

The F(ab')₂ portion of the immune and normal goat IgG was prepared by treating the IgG with pepsin, and the immune F(ab')₂ fragments were shown to bind to the MIA PaCa-2 in culture and inhibit their growth in culture and in nude mice; pretreating MIA PaCa-2 with the immune F(ab')₂ and injecting the viable cells resulted in both a significant delay in the appearance of the tumors and a reduction of the tumor size in the nude mice.

2. Sensitivity of MIA PaCa-2 to Chemotherapeutic Agents. We have previously described the sensitivity of MIA PaCa-2 to E. coli asparaginase. Our work in the past year has clearly demonstrated that the action of asparaginase was largely exerted through its L-glutaminase activity. Thus, Acinobacter asparaginase-glutaminase which possesses much more glutaminase activity than E. coli asparaginase is 50-100 times more potent in inhibiting MIA PaCa-2 growth than the E. coli enzyme. The new glutamine antagonist known as AT-125 has also been found very effective in vitro and has thus been extensively studied as to its mechanisms of action. Among these is the irreversible inhibition of -glutamyl transpeptidase.
3. Proteolytic Activity and Possible Role in Neoplasia. We have previously described the secretion of two proteolytic activities by MIA PaCa-2: A plasminogen activator which we have purified to homogeneity and a direct plasmin-independent protease. A membrane associated direct protease can be

Program Director: William E. Straile, Ph.D.

solubilized with Triton X-100. Recently in collaboration with Dr. Robert Rubin in the Department of Anatomy we have also found that the direct protease is very effective in hydrolyzing myosin--the skeletal protein of the cell. This discovery has provided us with a critically needed sensitive assay for the protease which now will hopefully enhance our efforts of this protease and possible relation to neoplasia will then become feasible.

Plans:

1. Purification of the tumor-associated antigen in human pancreatic cancer and its physicochemical characterization.
2. Devise a radioimmunoassay for use in detecting either the pancreatic antigen or its antibody in patients with the disease. It is hoped that the assay will detect the antigen and/or its antibody at an early stage in the disease.
3. Use the radiolabeled-IgG fraction (or the $F(ab')_2$ of the anti-MIA PaCa-2 for imaging of pancreatic cancer with computed tomography and nuclear scanning; initially, in the nude mouse model, and eventually in man.
4. Pursue the potential usefulness of glutamine antagonism in the chemotherapy of human pancreatic cancer.
5. Attempt to purify the membrane-associated protease and explore its possible usefulness as a biological marker of neoplasia.

Publications:

Allen, L., Meck, R. and Yunis, A.A.: Inhibition of glutamyl transpeptidase from human pancreatic carcinoma cells by (-S,5S)- -amino-3chloro-4,5-dihydro-5-isoxazal acid (AT-125; NSC, 163501). Res. Comm. Chem. Path. and Pharm. 27:175, 1980.

Grant 19188: Early Diagnosis of Pancreatic Cancer

From 07/01/77 to 08/31/81

FY 81: 0 (Ann. \$41,511)

Michael C. Geokas, M.D., Ph.D., Department of Internal Medicine, University of California School of Medicine, Davis, California 95616

Objectives: We have developed a two-dimensional slab gel electrophoresis system which utilizes the following advantages to visualize approximately 200 proteins in plasma: (1) high resolution two dimensional gel electrophoresis; (2) extremely sensitive silver stain or autoradiography technique; (3) removal of serum albumin via a column chromatography step. These techniques allow us to scan for small differences between the protein composition of normal plasma and plasma from patients with pancreatic cancer.

Accomplishments: We have developed the system described under objectives. To date, we have been unable to detect significant differences between the protein content of normal plasma and patient plasma.

Plans: We plan to continue to examine the reproducibility of the system to obtain better repeatability in order to scan for minor protein differences between normal plasma and patient plasma.

Program Director: William E. Straile, Ph.D.

Grant 19197: In Vitro Pancreatic Carcinogenesis

From 05/01/76 to 04/30/82

FY 81: \$61,618

Dr. Raymond T. Jones, Department of Pathology, University of Maryland School of Medicine, 10 S. Pine Street, Baltimore, Maryland 21201

Objectives: The overall objective of this project is to further study in vitro models of pancreatic carcinogenesis in order to provide a more rapid means of testing hypotheses relative to pancreatic cancer and to provide an important means of extrapolating from animal data to man. To do this we are studying chemical carcinogenesis of the bovine pancreatic ductal organ explant and cell culture models by various morphological and biochemical techniques. We have also developed explant models of the Syrian golden hamster pancreas and are studying them using similar techniques. In vitro studies using both organ explants and cell cultures are important in obtaining the primary goal of the Carcinogenesis Program in "preventing cancer in man by identifying environmental carcinogenic compounds and mixtures that may affect humans as well as by identifying the mechanisms of action of known carcinogens."

Accomplishments: Explant slices from the gastric lobe of adult Syrian golden hamster pancreas have been maintained in organ culture with preservation of both acinar and ductal cells for periods of 14 to 70 days. Histochemical and ultrastructural studies demonstrate the presence of zymogen granules in the acinar cells and mucus granules in the duct cells. A reproducible model system for the culture and study of adult exocrine pancreas has been developed. The cell of origin of pancreatic adenocarcinoma is unknown and in an attempt to elucidate this cell, sections of the gastric lobe of adult hamster pancreas have been treated with either N-methyl-N-nitro-N-nitrosoguanidine (MNNG) or N-methyl-N-nitrosourea (MNU) added to the culture medium (5.0 µg/ml MNNG or 2.5 µg/ml MNU). These studies demonstrate that morphologically dysplastic alterations can be induced in vitro and demonstrate a technique for the culturing of adult pancreas with the maintenance of both ductal and acinar cell types.

Plans: The development of the Syrian golden hamster pancreatic organ explant model has enabled us to further study pancreatic carcinogenesis. Now that we have exposed hamster explants to MNNG and MNU, we will expose them to specific carcinogens, such as BOP and BHP, that have been shown to cause pancreatic adenocarcinomas in the hamster. We will further study these explants as well as carcinogen-exposed bovine pancreatic cells and explants using morphological, biochemical and immunohistochemical techniques.

Publications: Jones, R. T., Hudson, E. A., and Resau, J. H.: A review of in vitro and in vivo culture techniques for the study of pancreatic carcinogenesis. Cancer, 47:1490-96, 1981.

Program Director: William E. Straile, Ph.D.

From: 06/30/76 to 04/30/82

FY 81: \$95,752

Dr. Levy Kopelovich, Memorial Sloan-Kettering Cancer Center, New York, NY 10021

Objectives: The objectives are to characterize the nature of an initiated cell through an analysis of the phenotypic and genotypic profile of cells from subjects with adenomatosis of the colon and rectum (ACR). Perturbation of these cells by tumor viruses and chemical and physical agents should aid in elucidating the mechanisms involved in cancer promotion and cancer control in man.

Accomplishments: Our findings suggest a systemic disorder of stromal cells in ACR individuals that might provide insight about carcinogenic mechanisms involving the large bowel. It is proposed that skin fibroblasts (SF) derived from normal-appearing biopsies of gene-carriers exist in an initiated state due to a dominant mutation. The genetic make-up of an initiated cell has been established through an analysis of concordance between the abnormal phenotypic markers and the pedigree profile and through cell hybridization, including initial analysis of gene products. We have demonstrated that these cells can be differentially transformed by oncogenic viruses, a carcinogen (MNNG), and γ -ray irradiation, and that they can be made to grow in vivo when exposed to a tumor promoter (TPA) alone. This simple experimental model provides a novel system for the study of tumor promotion in vitro. The apparent susceptibility of ACR cells to further transformation by oncogenic viruses and chemical and physical agents indicates that genetic information residing within these cells, probably in the form of a relatively limited and specific number of DNA sequences associated with the ACR mutation, renders them more sensitive to these three distinct classes of carcinogens. We submit that, through our tests on skin fibroblasts, ACR gene-carriers within recognized ACR clusters can be diagnosed at present with sufficient certainty to warrant immediate action. The identification of "risk profiles" might provide valuable information about cancer prognosis and cancer control.

Plans: We plan to establish and characterize the nude mouse system for the study of tumorigenicity of ACR cells treated with viral, chemical, and physical agents and establish a complete spectrum of tumor progression due to viral, chemical, and physical agents by comparing the phenotypic, metabolic, and genotypic profile of ACR cells and normal cells. Monoclonal methodology will be included. We propose to establish the genetic make up of an initiated ACR cell and a malignant ACR cell through use of linkage analysis, cell hybrids, organelle and DNA mediated-transfer in mock treated and virus or chemically treated cells. It is also planned to study the possible site within ACR cells which renders them more susceptible to transformation by all three classes of carcinogen, and we hope to establish additional biomarkers to distinguish ACR gene carriers and other cancer prone individuals.

Publications:

Chopan, M. and Kopelovich, L.: The Suppression of Tumorigenicity in Human x Mouse Cell Hybrids. I. Derivation of Hybrid Clones, Chromosome, Analysis, and Tumorigenicity Studies. Exp. Cell. Biol., 49:78-89, 1981.

Kopelovich, L.: The Use of a Tumor Promoter as a Single Parameter Approach for the Detection of Individuals Genetically Predisposed to Colorectal Cancer. Cancer Letters, 12:67-74, 1981.

Program Director: Vincent J. Carroli, Ph.D.

Grant 19272: Regional Trophoblastic Disease Center

From 06/30/76 to 06/30/82

FY 81: \$104,589

Dr. C.B. Hammond, Duke University, Durham, North Carolina 27710

Objectives: The objective of the Southeastern Regional Trophoblastic Disease Center is to enhance the available care for patients with malignant trophoblastic disease through expanded development of a regional center to provide clinical and laboratory expertise to aid community physicians who care for these patients.

Accomplishments: During the past nine months (July, 1980 - March, 1981), this center received 4,687 new physician contacts which resulted in 9,256 consultations with review of material and laboratory support. More than 13,000 serum beta-subunit hCG assays were performed for 4,785 patients presenting with hydatidiform moles. Forty patients with malignant gestational trophoblastic disease were treated at Duke, and 221 patients were treated elsewhere on a consultative basis. These patients represent 27 states and U.S. possessions.

Plans: Goals for the coming year include further expansion of the physician outreach program as well as investigation into the origins and treatment of gestational trophoblastic disease.

Publications:

Clayton, L. A., Tyree, L., Weed, J. C. Jr., Hammond, C. B.: Endocrine aspects of trophoblastic neoplasia. J. Reprod. Med., "in press," 1981.

Sink, J. D., Hammond, C. B., Young, W. G.: Pulmonary resection in the management of metastases from choriocarcinoma. J. Thorac. Cardiovasc. Surg., 1980.

Lewis, J. L. Jr., Hammond, C. B., Morrow, C. P., Stanhope, R.: How to diagnose, follow, and treat molar pregnancy. Contemp OB GYN, "in press," April 1981.

Hammond, C. B., Surwit, E. A.: Achieving a high cure rate for GTN. Contemp OB GYN, April 1981.

Program Director: Robert T. Bowser, Ph.D.

From 07/01/76 to 06/30/84 FY 81: \$30,743

Dr. Richard P. Elzay, Medical College of Virginia, School of Dentistry
Richmond, Virginia 23298

Objectives: The program is designed to improve cancer education for dental students, dental hygiene students, postgraduate students, faculty and practitioners beyond the content of the existing cancer program in the dental school curriculum through (1) educational programs directed toward the undergraduate students and graduates; (2) assisting in the maintenance of the Oral Tumor Registry, Computerized Oral Tumor Recall Program, Recall and Referral Clinic; (3) development and promotion of informational material available to practitioners and patients on Health-Line (Dial-A-Tape) program; (4) sponsorship of a continuing educational Oral Cancer Detection activity within the State of Virginia; (5) the continuation of an ongoing objective, orderly analysis and evaluation of the oral cancer curriculum within the School of Dentistry; and (6) special projects.

Accomplishments: (1) The development and administration of the Oral Tumor Registry, Computerized Oral Tumor Recall program, Recall and Referral Clinic. (2) Development of an ongoing self-evaluation diagnostic program for dental students. (3) Establishment of an annual continuing education program on oral oncology sponsored through the office of Continuing Education for practitioners in the State of Virginia. (3) Development and promotion of six Health-Line tapes giving informational services to practitioners and patients throughout the State. (4) Sponsorship of an annual Cancer Education-Detection Program alternating between Southwest Virginia, Eastern Shore and Northern Neck, Virginia financing six students and an Oral Surgeon and an Oral Pathologist to act as educators. (5) The hiring of a Curriculum Analyst to evaluate the undergraduate dental teaching curriculum with regard to oncology teaching efforts for dentistry and dental hygiene. (6) The production and publication of nine self-evaluation diagnostic cases published in the State Dental Journal for continuing education efforts of the practitioners. (7) Offering a core multidisciplinary course in oncology to the senior dental students. (8) Offering an oncology rotation in the hospital for dental and dental hygiene students. (9) Sponsoring two Clinical Assistants (Summer Fellows) to gain further educational experience in the areas of Oral Surgery, Oral Pathology and Maxillofacial Prosthodontics.

Plans: (1) Future activities would focus on promoting the use of the Health-Line services to practitioners and patients intramurally and extramurally. (2) Analyzing the data garnered from the Curriculum Analyst will help to institute realistic oncology objectives and develop courses for the dental and dental hygiene students which would meet these objectives. (3) A survey questionnaire would be disseminated to graduates of our program to ascertain what our weaknesses might be in the area of oncology education. (4) The development of the Oral Tumor Registry, Computerized Oral Tumor Recall program, Recall and Referral Clinic as educational instruments for undergraduate, graduate and postgraduate students will be continued. (5) Our continuing education efforts will be supported through an annual cancer program, self-evaluation examinations for dental students and self examination diagnostic cases for the practitioners in the Virginia State Dental Journal. (6) Our annual Oral Cancer Education-Detection program will be

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continued as an extramural activity for dental students in the State of Virginia.
(7) Two clinical assistantships for students to heighten their educational experiences in the areas of Oral Surgery, Oral Pathology and Maxillofacial Prosthodontics will be sponsored.

Grant 19344: Coping in Families with a Leukemic Child

From 06/30/76 to 06/30/81 FY 81: 0 (Ann. \$103,916)
Dr. Jerome Schulman, Children's Memorial Hospital, 2300 Children's Plaza,
Chicago, Illinois 60614

Objectives: Can families be helped to cope well with serious illness, with the results the prevention of psychological dysfunctioning, as well as growth and improved psychological health. This study is designed to provide a fuller understanding of the variables involved in healthy coping. In addition, a great deal of theoretical work has suggested approaches to intervention, but little has been done to test the effectiveness of interventions. The present study was developed to help families cope, based on data from healthy copers in a similar situation, and an experimental design was developed to test its effectiveness.

Accomplishments: 93 families of children with leukemia and meningitis have been seen as part of the project. Final assessments were completed and the last year of the project involves data analysis and publication of results. One book and one paper have been published, with one paper in press and three submitted for publication. Three more papers are in progress.

Briefly, most of the families were found to be coping well during the first six months and at one year post-diagnosis. Variables which correlated with coping at one year included age of child, coping of other family members, and occupational status of the father. Coping scores tended to be stable over time with continued high interrater reliability. At six months, mothers in the intervention groups were seen as coping significantly better than those in the control group by physicians, but these differences were not found at one year, when most of the children were doing well medically, and families may not have needed intervention.

Plans: Analysis of additional data (final assessments, child test data, content analysis, and clinical data) continues through year 5, and papers are being written and submitted for publication.

Publications:

Kupst, M.J. and Schulman, J.L.: The CPI subscales as predictors of parental coping with childhood leukemia. J. Clin. Psychol. (IN PRESS)

Program Director: Lawrence D. Burke

From 07/01/76 to 06/30/82 FY 81: \$103,973
Dr. R. Beverly Raney, Children's Hospital of Philadelphia
34th Street & Civic Center Blvd., Philadelphia, Pennsylvania 19104

Objectives: The program provides a wide range of clinical cancer education in Pediatric Oncology to students in the fields of medicine, nursing, social work, and dentistry, including undergraduates through full-time post-doctoral trainees planning a career in academic pediatric oncology. Through attendance at daily in-patient and out-patient conferences and observation of patients, students focus on the unique problems of the child with cancer and his family. Teaching also includes lectures, undergraduate student support for special projects, continuing education of practitioners at a weekly Tumor Board, and special conferences which summarize current multidisciplinary knowledge and indicate areas for future research.

Accomplishments: The core curriculum involves four specialized conferences per week in addition to those mentioned above: Oncology-Radiology, Adolescent Medicine-Oncology Management, Journal club, and Cancer Center Seminar. The latter two conferences are oriented toward clinical and basic research in oncology and are optional for students below the Clinical Associate level. Guest lecturers come from this country and abroad to present their research findings in cancer cell biology, epidemiology, etiology, genetics, late effects, and natural history and management of clinical cancer. We offer one to two-month electives in pediatric oncology at the undergraduate and graduate medical level, and participate annually in a multidisciplinary course in Oncology at The University of Pennsylvania School of Medicine. There are four Clinical Associates in Pediatric Oncology per year, who spend approximately half of their time in Oncology and the other half in pediatric hematology, bone marrow transplantation, and clinical and/or basic research. Each Associate is expected to contribute one or more articles per year for Medical and Pediatric Oncology, published in "Proceedings of the Tumor Board of the Children's Hospital of Philadelphia". The Clinical Assistants, expressed as full-time equivalents per year, consist of students in nursing (2), social service (1), dentistry (1), and medicine (2); their work involves assisting in clinical care and research projects under staff direction. A syllabus of review articles on selected major topics in Pediatric Oncology has been developed by Dr. Audrey Evans. The modes of evaluating efficacy of teaching are being explored by Mrs. Fergusson, head of the Pediatric Nurse Practitioner/Oncology Program, with help from Dr. Gregory Carroll in the University of Pennsylvania School of Education.

Plans: We will continue the activities cited above. We intend to broaden evaluative efforts by developing a questionnaire for previous trainees, to solicit suggestions for (1) changes in the program and (2) continuing education meetings. We are also developing a bank of multiple-choice questions in pediatric oncology, for us as guidelines for staff teaching and for pre-test evaluation of students' learning during their training.

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From 07/01/76 to 06/30/82 FY 81: 43,003

Dr. Jack E. White, Howard University College of Medicine
2041 Georgia Avenue, N.W. Washington, D.C. 20060

Objectives: The program is designed to enhance the cancer education of medical students, community practitioners, allied health workers and the public by providing clinical assistantships, elective core and elective curriculum in basic and subspecialty oncology, seminars, the demonstration of multidisciplinary care in tumor boards, conferences, grand rounds and annual symposia.

Accomplishments:

- (1) A ten week clinical assistants' summer work program with nine students and an academic year work program for five students were established.
- (2) The following are now well established parts of the program:
(1) tumor boards (weekly); (2) tumor conferences (weekly);
(3) annual Community Cancer Education Day Symposia; (4) clinical associates program; (5) nursing oncology program; (6) Community Outreach Program; (7) psychosocial programs for cancer clinical workers; (8) an oncology journal club; (9) 18 research seminars by guest lecturers between 9/10/80 and 5/21/81; (10) elective programs in radiation, medical, surgical and general oncology.
- (3) Cancer research building offers opportunities for basic research experience and epidemiological study and a clinical oncology unit. Clinical opportunities are functional.
- (4) National Board analyses are being provided this year for evaluation of students. This will be added to written papers required of clinical assistants and elective students increasing the significance of the evaluation process.
- (5) A syllabus on tumors of the head and neck, a continuing medical education film on recognition, evaluation and management of oral lesions and a Med/Com set on diagnosis of head and neck tumors have been developed.

Plans: Efforts will be made to: (1) obtain approval of the pending required core cancer course; (2) continue each existing program after evaluation and improvement; (3) increase the oncology faculty by one surgical and one medical oncologist; (4) obtain Howard University Hospital support for fourth and fifth-year postgraduate physician trainees; (5) produce additional teaching aids.

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From 07/01/76 to 06/30/82 FY 81: \$83,630
Dr. O. Ross McIntyre, Dartmouth Medical School
Hanover, New Hampshire 03755

Objectives: The objectives of this Clinical Cancer Education Grant are to improve cancer education at the undergraduate, graduate, and continuing education level at this Medical Center and in the surrounding region. The Cancer Education Committee responsible for the operation of the program has identified core skills and knowledge which it seeks to have recognized as an absolute requirement by the academic institution and the students alike. These include basic cognitive skills in such areas as tumor biology (for undergraduates) and cancer treatment (for housestaff), as well as psychomotor skills, where appropriate. In addition, the Committee arranges for and staffs outreach clinics and convenes conferences at the Center and throughout the region served.

In the development of each annual Medical Center plan, the Committee represents a larger number of individuals with interest in cancer education and serves as the focal point for allocation of institutional resources in this area.

Accomplishments: This year a new elective course in clinical nutrition was offered by an interdisciplinary team headed by Dr. Joseph O'Donnell, a member of the Cancer Education Committee. This course, which emphasizes nutritional aspects of cancer, will become a requirement in the four-year curriculum under development.

A program in psychiatric oncology is entering its second year. Dr. Ballantine, the clinical associate in psychiatry, provides clinical consultation to patients within the designated inpatient and outpatient cancer treatment area. He is assisting with a pilot study evaluating psychopharmacologic effects of cannabinal, a derivative employed as an anti-emetic. In addition, he provides psychological support services to the health care team assigned to the inpatient unit. In these activities he is supervised by Dr. Peter Silberfarb, who is a member of the Cancer Education Committee.

The genetic aspects of a familial cancer syndrome, multiple endocrine adenoma, is under investigation by Dr. Brain Quinn, a clinical associate. A kindred with this syndrome was discovered in patients with medullary carcinoma of the thyroid from a large family of French-Canadian extraction who were studied at our institution. The family may be the largest one yet studied, and Dr. Quinn is working with a team of Cancer Center investigators to seek improved means of detecting the 50% of the family members at risk.

An improved communication, Cancer Quarterly, has been developed in the past year and is mailed to 1,500 physicians and other health care professionals in the region. While financed by other sources, members of the Cancer Center staff contribute to its content, which provides information to the recipients concerning the results of treatment trials, new diagnostic tests, and other similar information.

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The Cancer Education Committee continues to provide critique of the curriculum with respect to cancer. While the most dramatic achievement has been the recognition of need for an orgnized presentation of subject matter to nutrition, other

areas have also received attention. The timing of the introductory course in oncology has been further refined and new faculty recruited to staff this multidisciplinary offering. The principal addition here has been Dr. Christopher Coughlin, a new faculty member in Radiation Oncology.

Plans: While continuing the activities mentioned above and developed new programs to suit the needs of the undergraduate curriculum, the major activity for 1981 will be the organization and offering of a postgraduate course entitled "Oncology in the Eighties." This course will be given during August of 1981 and draws upon faculty from this Medical Center, as well as other cancer treatment centers throughout the country. It is anticipated that this course will be attended by 150-200 persons drawn from students and practicing physicians nationwide.

Grant 19381:

Clinical Cancer Education Program

From 07/01/77 to 06/30/84

FY 81: \$59,719

Dr. Irwin H. Krakoff, University of Vermont College of Medicine,
Burlington, Vermont, 05401

Objectives: The objectives of this cancer education program are to further the teaching of all aspects of cancer as a comprehensive clinical discipline to medical students and nurses and, crossing traditional specialty boundaries, to house officers, subspecialty trainees and physicians throughout the Vermont region.

Accomplishments: (1) The Vermont Regional Cancer Center has been organized and is a functioning extra-departmental unit of the College of Medicine, with Dr. Krakoff as its Director. (2) Six additional oncologists have been added to the faculty, two each in medical oncology and radiation oncology, one in gynecology, and one in pathology, (3) The format of the Tumor Board has been up-graded resulting in increased attendance. (4) The expansion of clinical investigations and studies of pharmacodynamics has strengthened teaching of students, houseofficers and fellows. (5) There has been a marked increase in continuing education throughout the region. (6) The Interact TV Network has been instrumental in upgrading nursing practices in outlying hospitals and nursing homes. (7) The Basic Mechanisms of Disease course has been replaced by a Senior Major Program, and each clinical rotation now contains an oncology segment. (8) Outstanding lecturers have been sponsored on cancer topics.

Plans: It is planned to offer graduate education programs in three specialties (medical oncology, pathology, and psychiatry), to expand an oncology nursing education program, to provide faculty attendance and participation at local and regional Tumor boards and conferences, and to resume the guest lecture series and student assistantships. An Instruction Evaluation Service would develop methods and instruments for evaluation of the programs.

Program Director: Margaret H. Edwards. M.D.

Grant 19410: Studies of the Histogenesis of Pancreatic Carcinoma

From 05/01/76 to 04/30/83

FY 81: \$88,317

Dr. Daniel S. Longnecker, Department of Pathology, Dartmouth Medical School,
Hanover, New Hampshire 03755

Objectives: This series of studies bears directly or indirectly on the question of histogenesis of carcinoma of the pancreas in humans. Specific objectives include: (1) to critically assess the significance of focal acinar cell dysplasia in the human pancreas by refining analyses of the series of human pancreases which have been prospectively collected as part of this project during its initial four years; (2) to search for clues regarding the histogenesis of pancreatic carcinoma by electron microscopic studies of a series of such cancers; (3) to evaluate the reversibility of focal acinar cell dysplasia in rats; (4) to compare the histologic types of neoplasms which arise from acinar cells and from ductal cells in appropriate animal models, and to compare these experimentally induced cancers to the histologic types of human carcinoma.

Accomplishments: Foci and nodules of dysplastic acinar cells have been described in the human pancreas. These lesions are composed of circumscribed groups of phenotypically altered acinar cells that were recognized because of one or more of the following differences from surrounding "normal" acinar cells: (1) reduced cytoplasmic basophilia; (2) reduced cytoplasmic mass; (3) reduced zymogen content; (4) cytoplasmic vacuolization, and (5) nuclear enlargement and/or pleomorphic confirmation. Some of these lesions appeared similar to focal acinar cell lesions induced in experimental animals by pancreatic carcinogens. We have examined 276 human pancreases obtained at autopsy to detect such lesions by screening 10-12 sections per pancreas. More than half of the pancreases were found to have focal acinar cell dysplasia. The prevalence of lesions is higher in adults than in children, but there is not a positive correlation of increasing age and prevalence among adults. The high prevalence suggests that most such lesions are not "pre-malignant," and suggests that some of the lesions may be reversible. Animal studies have been initiated to evaluate nodule reversibility; to compare the effect of the pancreatic carcinogens azaserine and N-nitroso-bis-(2 oxopropyl)amine in a single susceptible species, and to compare the histogenesis of pancreatic neoplasms induced in a single species by "acinar cell" and "ductal cell" carcinogens. A series of 160 azaserine-induced pancreatic cancers in rats have been histologically classified and compared with the histologic types of human pancreatic cancer. In this animal model we believe that all pancreatic tumors arise from acinar cells, and the majority of tumors have been classified as well-differentiated or poorly-differentiated acinar cell carcinomas. However, among these tumors we have identified six histologic patterns including ductlike, cystic, and undifferentiated areas. This demonstrates that tumors of diverse histologic type result when rats are treated with an "acinar cell" carcinogen. Collection of electron micrographs of human pancreatic cancers from several centers is in progress.

Plans: Goals for the future are largely dictated by current activity since each of the studies is longterm. We plan to complete evaluation of the dysplastic acinar cell and ductal lesions in the human autopsy series. Increasing emphasis will be placed on study of the ultrastructure of human pancreatic carcinomas. One new longterm animal study will be initiated to try to identify a single

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species in which both "acinar cell" and "ductal cell" carcinogens are effective. This will be a study of the effect of N- δ (N-methyl-N-nitrosocarbamoyl)-L-ornithine in the hamster.

Publications:

Longnecker, D.S., Shinozuka, H., Dekker, A.: Focal acinar cell dysplasia in human pancreas. *Cancer* 45:534-540, 1980.

Longnecker, D.S. and Webb, J.N.: Dysplastic acinar foci in human pancreas (Letter). *Human Path.* 11:86-87, 1980.

Shinozuka, H., Lee, R.E., Dunn, J.L., and Longnecker, D.S.: Multiple atypical acinar cell nodules of the pancreas. *Human Path.* 11:389-391, 1980.

Longnecker, D.S., Hashida, Y., and Shinozuka, H.: Relationship of age to prevalence of focal acinar cell dysplasia in human pancreas. *J. Natl. Cancer Int.* 65:63-66, 1980.

Maloy, A.L., Longnecker, D.S., and Greenberg, E.G.: The relation of islet amyloid to clinical type of diabetes. *Human Path.*, in press.

From 07/01/76 to 06/30/82

FY 81: 83,668

Dr. Edward W. Browne, Jr., Meharry Medical College, School of
Medicine, 1005 18th Avenue North, Nashville, Tennessee 37208

Objectives: This program is designed to foster the development of a multidisciplinary, multilevel cancer education program for undergraduate medical students, residents in the usual clinical disciplines and practicing physicians. This is accomplished through: (1) a program of curricular assessment and evaluation; (2) provision of clinical assistantships during summer experiences for undergraduate medical students; (3) strengthening a core curriculum in oncology; (4) expanded involvement of the medical school departments in the oncology curriculum; (5) providing patient care in a multidisciplinary setting and (6) providing continuing education in oncology to undergraduate students, residents, faculty and staff.

A variety of pedagogical techniques are employed to increase knowledge and understanding of the fundamental principles of cancer biology and improve skills in the utilization and performance of procedures useful in the early detection and diagnosis of cancer in an effort to establish more realistic attitudes on the part of health care providers toward cancer, and establish motivation for continued study to upgrade clinical skills in cancer prevention, detection and management.

Accomplishments: The discrete activities presently receiving support under this grant are as follows: (1) ongoing curriculum assessment and evaluation of oncology teaching as a consequence of which a cancer examination assessing cognitive data and affect with regard to cancer care is being developed; (2) development of an 18-hour Introduction to Oncology course in the sophomore year; (3) development of a strong multidisciplinary summer clinical assistantship program for ten students for two months each summer; (4) development of a series of oncology grand rounds directed at students, housestaff, faculty and practitioners utilizing both on campus expertise and that of guest lecturers; (5) development of a psychological support team and strengthening the program in rehabilitation for oncology patients; (6) development of an annual half-day symposium in oncology primarily directed at practicing physicians in conjunction with an annual surgical symposium; (7) development of an oncology library in the clinical cancer education office available to students and housestaff in the hospital. The numbers and types of persons benefitting directly from these various educational activities are as follows: 125 second year medical students in the Introduction to Oncology course, ten rising junior students in the summer clinical assistantships, 25-30 medical students, residents and staff for each session of oncology grand rounds presented nine times yearly, and 50-75 medical students, residents, staff and practicing physicians in the annual cancer symposium. Additionally, other activities that are rendered more meaningful as a consequence of the grant are the tumor seminar in which 100-125 third year medical students parti-

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cipate for a period of eight weeks each, weekly tumor conference directed at 10-15 medical students, residents and oncology staff, oncology electives in medicine and surgery for 20-30 fourth year students per year and twice weekly tumor clinic involving approximately ten oncology staff, residents and medical and dental students. The summer clinical assistantship is a multidisciplinary experience; each student is required to produce a manuscript on some aspect of cancer diagnosis and/or management.

Plans: In the current year it is planned to continue the activities detailed above with refinement particularly of the cancer examination planned for longitudinal assessment of progress of our students, continued improvement of the course Introduction to Oncology, and further expansion of the satellite cancer library. Attention will continue to be focused on efforts at improving evaluation both of oncology teaching and student resident performance.

From 07/01/75 to 06/30/84 FY 81: \$144,625

Dr. David N. Orth- Vanderbilt University Cancer Research and
Training Center, Nashville, Tennessee 37232

Objectives: The specific objectives of CANCEP include increasing the visibility of clinical oncology in the Medical Center and the community and stimulating increased interest in and understanding of the fundamental nature of cancer and its diagnosis, treatment, and control; the further development of a highly-structured Core Curriculum of lectures, seminars, and conferences; the development of an Elective Curriculum consisting of a full array of associated clinical cancer specialty programs within the Medical Center and designed to complement the Core Curriculum for medical students, housestaff, predoctoral Clinical Assistants, and post-residency Clinical Associates in the CANCEP programs; and presentation of on-campus courses and seminars and outreach programs to enable the practicing physician to keep himself abreast of current developments in clinical cancer.

Accomplishments: Improving the cancer education program at Vanderbilt, including supporting a core curriculum, and elective curriculum, clinical oncology grand rounds, and continuing education; an elective course for first-year medical students, "Basic Concepts in Cancer," initiated the program, the second-year required "Neoplastic Disease" and elective "Clinical Oncology" course built upon this, and Oncology Grand Rounds provided the vehicle for educating third- and fourth-year medical students, house officers, nurses and staff. CANCEP faculty taught in the clinical setting on four in-patient oncology consulting services and in almost a dozen out-patient clinics each week. The psychosocial effects of cancer on the patient and his/her family were taught through an undergraduate course entitled, "Death and Dying," through rounds and clinics conducted by a faculty psychologist with pediatric hematology-oncology, and through a lay-oriented organization called ALIVE, in which CANCEP faculty are very active. Continuing education was promoted through an on-campus symposium entitled, "Ovarian Carcinoma; Review of Recent Developments" for which two of five visiting faculty were supported. CANCEP faculty produced a regular feature of the JOURNAL OF THE TENNESSEE MEDICAL ASSOCIATION called, "Oncology Grand Rounds," and gave lectures to physicians and staff of many area hospitals this past year. CANCEP supported five Clinical Associates, three of whom did clinical research in medical oncology, one of whom did clinical research in oncologic pathology. Sixteen Clinical Assistants were supported, most of whom carried out clinical research and three of whom did laboratory research project; several publications are in preparation, in press, or in print as the result of their studies. A syllabus in gynecologic oncology was developed with CANCEP support, and post-course student evaluation questionnaires were used to redesign portions of the cancer curriculum.

Plans: We will gradually be shifting the emphasis of our program from postdoctoral training of oncology specialists to providing all graduating medical students with a sounder background in oncology, involving them in clinically-oriented research projects to teach them a healthy skepticism for what they read in the literature. We will also continue to serve as a regional resource for the continuing cancer education of physicians in a variety of clinical disciplines.

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From 07/01/78 to 06/30/84

FY 81: \$50,676

Dr. Sandra Ginsberg, M.D., SUNY-Upstate Medical Center

750 East Adams Street, Syracuse, NY 13210

Objectives: The program is designed to (1) develop a coordinated, multidisciplinary educational program directed toward medical students in both the preclinical and clinical years, clinical associates, faculty, practitioners in the community, and allied health professionals; (2) develop tools to allow ongoing evaluation of the impact of this broad educational program and (3) expand the existing programs in medical, surgical, gynecologic, and radiation oncology and develop a program in pediatric oncology.

Accomplishments: (1) The interdisciplinary oncology faculty is involved in medical student education at the preclinical level through provision of clinical correlations relevant to cancer and through the required Introduction to Clinical Oncology lecture series. (2) During the mandatory clinical curriculum the screening, diagnosis, epidemiology, evaluation, staging, and treatment of patients with cancer are stressed during lecture series, daily rounds, conferences, and clinic experiences. The importance of an interdisciplinary approach and of well-conducted clinical trials are emphasized. (3) An active oncology elective program for medical students has been established. A series of videotapes provides a core-curriculum for all students taking oncology electives and computerized clinical diagnosis quizzes provide interactive instruction. (4) Intensive and continuous cancer education is provided to our residents through extensive exposure to the expanded inpatient and outpatient oncology services. (5) The clinical associates in medical hematology/oncology, pediatric hematology/oncology, gynecologic oncology, and radiation oncology are simultaneously the recipients of and major contributors care and clinical research activities, they provide education to patients, house officers, allied health professionals, and other physicians. (6) An active continuing education program for physicians, which includes weekly conferences, regional and national lecture programs, cancer research seminars, clinical diagnosis quizzes, and a patient and community physician oriented outreach program, has been established. (7) Educational programs for allied health professionals, including formal and informal lectures and conferences for nurses and an oncology pharmacy educational program for undergraduate and graduate pharmacists, have been organized. (8) The addition of cancer-related questions to the tests given after each segment of the mandatory curriculum, pre- and post-elective testing of students taking oncology electives, and an attitude survey have been implemented to allow evaluation of the impact of our total undergraduate cancer education program.

Plans: (1) To have greater impact on the most formative years of medical student training we will: increase the involvement of the interdisciplinary oncology faculty in teaching during the preclinical years; expand the Introduction to Clinical Oncology course; and use the interdisciplinary oncology clinic in teaching physical diagnosis. (2) New interdisciplinary programs will be offered: a dental oncology program, and an oncology pharmacy clinical associate position.

Program Director: Margaret H. Edwards, M.D.

From 07/01/76 to 06/30/82

FY 81: \$,122,798

Dr. Charles L. Spurr, Bowman Gray School of Medicine of Wake Forest University
300 South Hawthorne Road, Winston-Salem, North Carolina 37103

Objectives: The multidisciplinary Cancer Education Program has the following goals: (1) development and promotion of a balanced academic program in oncology teaching, research and exemplary care throughout the institution and among the profession in our region; (2) to coordinate and supervise undergraduate and postgraduate education in accurate preventive, diagnostic and therapeutic oncology; (3) to encourage undergraduate participation in cancer research; (4) to provide comprehensive training for residents entering specialized areas of cancer care and research; (5) support cancer patient education; (6) promote and support cancer education by health educators throughout the region; (7) to promote a more comprehensive public cancer education program.

Accomplishments: (1) a) Development of interdepartmental cancer conferences; b) development of the Piedmont Oncology Association - a regional collaborative oncology group made up of 70 oncologic specialists with the principal objective of clinical cancer trials and cancer education through multimodality cancer treatment protocols, quarterly meetings with educational sessions, and an annual oncology seminar with outstanding national investigators; c) development of the Piedmont Oncology Nurses Association composed of 87 oncology nurses with a goal of exemplary cancer patient care. (2) a) Development of an undergraduate oncology module for second year medical students composed of 24 hours of instruction by a multidisciplinary Medical School faculty; b) coordination of an additional 13 hours of oncology instruction in the second year; c) instruction and supervision of third and fourth year medical students and house officers in cancer patient care via both very active inpatient and outpatient services. (3) Coordination and supervision of approximately nine medical students yearly as cancer research clinical assistants in cancer related research in microbiology, medical oncology, surgical oncology, urology, gynecologic oncology. (4) Subspecialty training of board-certified internists in medical oncology to insure that the best possible care is available to cancer patients within our region. Presently two to three clinical associates are in training in each of the two years required for board certification. (5) Development of a cancer patient support and counseling program which involved training volunteers from the community in the counseling and education of cancer patients. (6) Organization of cancer education activities among health educators in the northwest region of N.C. and preparation of resource manuals to assist them. (7) Development, in association with the ACS, of a cancer education effort directed toward the black community.

Plans: (1) Continuation of POA and POA Nurse programs with intensified attention toward accurate and timely intragroup communication. (2) Further refinement of undergraduate oncology module to include material developed in conjunction with cancer prevention for physicians assistants. (3) Continuation of clinical assistantship program in cancer research. (4) Completion of subspecialty training for three second year clinical associates and initiation

Program Director: Margaret H. Edwards, M.D.

of training for three first year associates. (5) Further refinement of cancer patient support program and development of intrainstitutional multispecialty cancer patient support program. (6) Attempt to draw together the POA and educational outreach activities for nurse and lay groups in order to develop a more comprehensive public education program. (7) Further development of black community program.

Grant 19460: Cancer Control Program for Family Practitioners

From 06/30/76 to 06/30/81

FY 81: 0 (Ann. \$185,000)

Dr. J. T. Painter, M. D. Anderson Hospital and Tumor Institute, 6723 Bertner Avenue, Houston, Texas 77030

Objectives: This program is designed to introduce the family practitioner to his role in cancer detection, diagnosis, treatment, rehabilitation, and continuing care through, 1) elective training programs to broaden the availability of professional personnel skilled in aspects of cancer care; 2) training periods for residents in family practice programs in community hospitals; and 3) extrainstitutional programs given at family practice training hospitals in Texas. An awareness of cancer as a disease and public health problem is created at the community level.

Accomplishments: Through the establishment of both an intrainstitutional and an extrainstitutional demonstration training program, an effective mechanism has been provided to teach the necessary expertise to the family practitioner which will enable him to respond directly to the needs of patients with long term illnesses from cancer. The program emphasis has been on the training of the new physician who is on the verge of assuming his role as a family practitioner. The one-month elective rotation allows the residents access to the faculty expertise and facilities of M.D. Anderson Hospital. The rotation consists of two weeks in M.D. Anderson's gynecology and gastroenterology clinics. Knowledge and understanding in these areas are gained through direct observation, didactic information and clinical experience. Between October 1, 1980 and June 30, 1981, 14 residents will have been trained under this program. The total number trained through June 30, 1981 is 120 residents from eight family practice residency programs in Texas, New Mexico, and Louisiana. It is anticipated that this program can serve as a model for similar programs elsewhere. It does appear that the basic model has been tested sufficiently for this purpose and that other means of support should now become available.

Plans: This demonstration training program has been undergoing an orderly phaseout. A final report will include an evaluation of trainee experience, an analysis of the problems encountered in the development of the program, the approaches used to bring the program to its present level of success and other pertinent information which may be useful to others starting similar programs.

Program Director: Dorothy R. Brodie, M.D.

From 01/01/75 to 06/30/82

FY 81: \$142,300

Dr. B.J. Kennedy, University of Minnesota School of Medicine,
Minneapolis, Minnesota 55455

Objectives: This Clinical Cancer Education Program augments training and education in neoplastic diseases. It is aimed at increasing knowledge about cancer for medical students, residents, specialists in oncologic specialties and oncology nurses. Part I provides an internship program for medical students in Medical Oncology, cancer training of medical residents, and augments the cancer education of physicians specializing in Medical Oncology. Part II supports a multidisciplinary effort to provide medical students an opportunity to expand their learning in oncology and to develop new programs in oncology education. Both parts contribute to the cancer education of medical students from three medical schools.

Accomplishments: Under the guidance of the Cancer Education Committee sponsored by this grant the following cancer education activities are conducted beyond the scope of the regular medical school curriculum: (1) An inpatient course for medical students in Medical Oncology where the students act as interns (26 this year) and participate in the interdisciplinary cancer course. (2) An interdisciplinary cancer course, "Diagnosis, Evaluation, and Care of Adults and Children with Cancer." (3) Cancer seminars in clinical oncology conducted twice a week for medical students and residents with lectures by clinical associates, oncology faculty and invited speakers. (4) Weekly Pathology Conference and Tumor Conference for medical students. (5) Participation of Clinical Associates in Medical Oncology in cancer teaching conference for students, residents, continuation courses, and community cancer programs. (6) Development of a monthly list of references on "Current Concepts in Cancer" for distribution to medical students. (7) Two cancer conferences for medical students planned by student members of the Cancer Education Committee with attendees from three Minnesota medical schools. (8) Special lectures by grant-supported-faculty on a variety of cancer subjects. (9) Guest lectures for special topics in oncology. (10) Encouragement of medical students to participate in cancer research. (11) Participation of faculty and students in the psychosocial cancer program called "Living with Cancer." (13) Participation of cancer-education-faculty and clinical associates in national programs relating to cancer education. (14) Participation in research relating to medical (cancer) education.

Plans: During the next year this program will increase medical student participation in the elective cancer courses. There will be greater student participation in planning cancer conferences for medical students. Clinical associates will be developed for academic careers in oncology. Faculty participants will develop outreach programs in oncology for community physicians. Efforts to develop a core curriculum in cancer will be continued.

Program Director: Margaret H. Edwards, M.D.

From: 07/01/76 to 06/30/82

FY 81: \$59,215

Alvin L. Watne, M.D., West Virginia University School of Medicine,
Morgantown, West Virginia, 26506

Objectives: The objectives of the Clinical Cancer Education Program are to (a) enable medical students to acquire an understanding of fundamental principles of cancer biology, epidemiology, detection, diagnosis, treatment and control, (b) establish attitudes and motivation for continued learning about cancer which will carry over into their postgraduate years, and (c) develop concepts of comprehensive multidisciplinary and humane care for a type of patient whose problems are sometimes discouraging psychologically and socially disruptive.

Accomplishments: A Personalized System of Instruction has been developed for the Basic Cancer Course and a progressive multiple baseline achievement test administered which determined that the students' examination performance increased after exposure to the instructional package. The modified PSI course with slide/tapes was implemented with students viewing them and reviewing study guides. The Clinical Assistant program was structured with a basic science and clinical preceptor and defined objectives were made available and refined. The education consultants began a study of all the senior oncology electives to work with the faculty on developing clear-cut objectives and a system approach for achieving and evaluating the elective. The Cancer Committee at West Virginia Medical Center has participated in a clinical cancer training program since 1963. During that time they have provided the core curriculum and medical student education, including the Annual Cancer Teaching Days featuring guest lecturers and the cancer faculty. A Clinical Associate was recruited who acts as the coordinator of the multidisciplinary weekly Tumor Conference. The Basic Cancer Course was offered as an elective to the first and second year medical students. Seventeen students participated in this elective during the fall session and 15 in the winter session. Five Clinical Assistants completed summer projects in a variety of programs including the review of cytopathology material involving primary tumors of the lung, a clinical and pathological study of all children with neuroblastoma at West Virginia University, the radiological study of carcinoma of the pancreas, the purification of human lung tumor antigen and the study of the role of various hormones in the regulation of glucose metabolism in rat hepatocytes, which will be presented at the School of Medicine Research Symposium.

Plans: The following educational activities have been undertaken and will be continued through the current year: editing and production of the Basic Science Course, instructional manual and student body guide, both for use at West Virginia University, and other institutions; continuation of the guest speakers for continuing education programs; implementation and evaluation of PSI for Laboratory and Clinical Assistantships; and structure objectives for Clinical Associates in Medical and Surgical Oncology and conduct cancer attitude survey for medical students, faculty and follow-up of prior trainees.

Program Director: Margaret H. Edwards, M.D.

Grant 19532: Clinical Cancer Education Program (Dental)

From 07/01/76 to 06/30/82

FY 81: \$48,398

Dr. Gird A. McCarty, Jr., University of Tennessee College of Dentistry
875 Union Avenue, Memphis, Tennessee 38163

Objectives: This cancer education program is designed to develop and maintain an active, coordinated approach to cancer education for the dental community, and to increase the competence of dental students in oral cancer screening, biopsy, and cytology teachings and to promote their use in routine practice. Increased experiences will be provided for students in the management and treatment of oral cancer, and they will have opportunities to become more proficient in the dental management of patients receiving radiotherapy and chemotherapy. Students will also participate in maxillofacial prosthetic rehabilitation procedures.

Accomplishments: During the past year, 300 undergraduate dental students have participated in applying screening procedures (including biopsy and cytology techniques) to 6,000 clinic patients. The Maxillofacial Prosthetic clinic has served as a training site for residents in oral surgery, pedodontics and periodontics, and for dental students and practicing dentists. The 20-hour oncology lecture course reaches 150 senior dental students and 50 practicing dentists participated in continuing education activities. Audiovisual aids (a slide-tape series on oncology) is used by both dental students and dental practitioners.

Plans: The ongoing activities will be continued and expanded. The oncology lecture series will be increased to 24 hours. Screening and maxillofacial activities will be continued. Evaluation plans are underway to assess the effectiveness of the four-year curriculum that recently has been reinstituted.

Program Director: Margaret H. Edwards, M.D.

From 07/01/76 to 06/30/82 FY 81: \$44,869
Dr. Benjamin F. Rush, Jr., New Jersey Medical School
100 Bergen Street, Newark, New Jersey 07103

Objectives: This program is designed to 1) coordinate the cancer education activities in six teaching hospitals in the greater Newark area; 2) develop better techniques to evaluate student attitudes towards cancer and acquired cancer knowledge during the four years of medical school under this program; 3) enrich the curriculum with additional cancer courses and electives; 4) support special student projects in cancer research; 5) improve our program of continuing education for practitioners; 6) increase multidisciplinary cancer teaching opportunities for students and practitioners; 7) enhance medical students' ability to recognize early oral cancer lesions as well as all other common neoplasms.

Accomplishments: 1) We have developed a successful liaison between our six institutions with monthly meetings of the cancer coordinators of each institution. 2) We have developed a questionnaire to be used for student evaluation. 3) Two student syllabi have been developed and distributed to all of our medical students one for the first two years of medical school and the other for the last two years. 4) A weekly cancer series of lectures and demonstrations and head-and-neck cancer with emphasis on the early oral lesion is being conducted. 5) An all-day seminar with an audience of several hundred students and practitioners on "Cancer in Newark" was conducted with the participation of Department of Preventive Medicine. 6) A series of 12 lectures by distinguished speakers has been supported under the auspices of the New Jersey Cancer Club, and the Departments of Surgery and Medicine of the New Jersey Medical School. 7) We are preparing the grant eight summer research scholarships in cancer to our medical students this coming summer and six students last summer completed such programs. These programs dealt with such problems as the epidemiology of cancer in Newark, regional versus systemic, chemotherapy in an experimental tumor system, construction of a new larynx in patients following laryngectomy, effect of bleomycin and cis-hydroxymoline on hamster lungs, the effect of histones on activity of the oxyribonucleoside of the oxyribonucleoside derived from mouse melanoma cells, stomach cancer morbidity in New Jersey 1949-1976, the study of pre-menopausal breast cancer and investigation of contraceptive history in both groups, progress in evaluating brush and forceps biopsies as diagnostic aids in suspected peripheral versus central bronchogenic carcinoma, and comparison of puromycin aminonucleoside uptake in normal and transformed human lung fibroblasts.

Plans: In the coming year we plan to evaluate our cancer test for students and to assign cancer patients to members of our incoming class of students. The two cancer syllabuses will be reviewed and updated. The development of computer links and possible T.V. links between our interhospital group will be developed.

Program Director: Margaret H. Edwards, M.D.

From 07/01/79 to 06/30/82

FY 81: 57,697

Dr. J. Tate Thigpen, University of Mississippi Medical Center,
2500 North State Street, Jackson, Mississippi 39216

Objectives: This program is designed to improve clinical cancer education in the State of Mississippi through six specific objectives: (1) the establishment of an administrative unit at the University Medical Center to coordinate all levels of cancer education; (2) the development of an innovative approach to cancer education for medical students (coordinated lectures, written materials, case presentation conferences, and patient contact); (3) the expansion of interdepartmental activities in cancer education for residents and fellows at the University Medical Center; (4) the development of effective continuing medical education symposia and seminars on cancer for Mississippi physicians; (5) the sponsorship of paramedical symposia on cancer; and (6) the development of an Oncology Syllabus and self-assessment materials for all program participants.

Accomplishments: (1) An administrative unit dealing with cancer education has been established at the University Medical Center (UMC). This unit works with four advisory committees: Intramural Clinical Cancer Education Committee (governing activities at UMC), Regional Cancer Advisory Committee (relating to continuing medical education), and two paramedical advisory committees (dealing with nursing and pastoral education in cancer). These committees together with the unit coordinate all program activities. (2) A coordinated cancer education program for medical students has been established. An introductory lecture series to second-year students is supplemented by case-presentation conferences in the third year and an interdisciplinary elective in the fourth year. The recommended fund of factual information is provided to all students in the format of the Oncology Syllabus. (3) Interdisciplinary conferences on cancer for residents and fellows have been established in a coordinated fashion, and fellow rotations through other departments have been established to enrich the fellowship experience. (4) Continuing medical education for the practicing physicians in Mississippi has been established. Semi-annual two-day symposia provide quick update on specific subjects in oncology. Seminars for hospital staff meetings, area medical association meetings, and local hospital tumor boards have been provided upon request and encouraged. (5) Paramedical symposia in cancer have been provided for nurses (two per year) and those engaged in pastoral care (one per year), and a clinical pastoral residency program has been established at UMC. (6) An Oncology Syllabus is now essentially complete and forms the factual basis of all parts of the program.

Plans: The third year of this grant will be the first in which all programs will be fully active. Plans for this year include: (1) a careful assessment of current programs in an attempt to identify deficiencies and additional needs; (2) expansion of the fourth-year student elective; (3) an increase in fellowship program activity; (4) expansion of outreach seminars in the state; and (5) consolidation and continuation of symposia for physicians and paramedical personnel.

Program Director: Margaret H. Edwards, M.D.

From 07/01/76 to 06/30/82

FY 81: 89,110

Dr. Henry M. Lemon, University of Nebraska Medical Center
Omaha, Nebraska 68105

Objectives: The cancer education grant is aimed at improving undergraduate and postgraduate education in prevention, diagnosis, treatment and rehabilitation of cancer in the upper Missouri Valley area, in eastern Nebraska and western Iowa. The objectives include improved undergraduate education in cancer through analysis and presentation of "cured" cancer patients to basic science courses, improved undergraduate and graduate training in internal medicine in cancer prevention, earlier detection and improved multidisciplinary treatment in pediatric, medical, radiologic, surgical and gynecologic oncology at the Medical Center campus and in three remote consultation clinics and seminars held monthly at outlying hospitals in Nebraska and Iowa.

Accomplishments: The primary accomplishments of the educational program have been the development and maintenance of excellent teaching services, both in the basic sciences and in gynecologic, pediatric, radiologic and medical oncology. The program is conducted in a multidisciplinary medical center, embracing a variety of public and private hospitals, centered in the University of Nebraska Hospital. Annual revision of the Chemotherapy Manual used by the Medical Oncology Section of the Department of Internal Medicine has been done so as to include the best programs of chemotherapy of cancer, and periodic updating of the results of these protocols has been carried out. Physician continuing education in all aspects of cancer has been pursued with monthly luncheon seminars at each of three community hospitals, in addition to the continuing weekly interdepartmental tumor conferences, biweekly gynecologic oncology conferences and sectional seminars in the medical oncology section.

A Hospice Without Walls is now functioning at the Medical Center and plans have been developed for a free-standing unit which will emphasize the teaching of medical and paramedical personnel in the midwest.

Additional clinical associates have begun their training during the current year. The Medical Oncology Section co-sponsored favorably a bill to make cancer a state-wide reportable disease in Nebraska, for educational and scientific purposes. An Oncology Journal Club jointly sponsored with Creighton University faculty is now in its fourth year of operation, to provide resident, clinical associate and faculty continuing education. A 13-year long project in breast cancer prevention is being completed this year, with the completion of a text on "Prevention of Breast Cancer".

In addition to the Gynecologic Oncology Group, we have been accepted in the North Central Cancer Treatment Group for prospective clinical trials. Two scientific exhibits were presented at the Omaha Midwest Clinical Society Meeting in October 1980 on "Chemotherapy or Small Cell Carcinoma of the Lung", and "An Evaluation of the Accuracy of Liver Scans in Detection of Metastatic

Program Director: Margaret H. Edwards, M.D.

Disease", which received premier awards in their categories of exhibits. Three scientific abstracts have been accepted for presentation at the 1981 spring meetings of the Endocrine Society and at the American Association for Cancer Research, in addition to seven accepted or published papers. Several students have accomplished research programs through grant support.

Plans: During the forthcoming year, it is planned to re-develop a core curriculum for all of our students in cancer prevention, detection, treatment and rehabilitation, and introduce it as an integral part of the new four-year curriculum. In addition, we will maintain the excellence of our current operations with appropriate performance audits.

Grant 19681: Psychosocial Collaborative Group for Cancer Control

From 04/16/79 to 03/31/82 FY 81: \$177,102
Dr. Arthur Schmale, University of Rochester, Medical Center, 300
Crittenden Boulevard, Rochester, New York 14642

Objectives:

1. To utilize the resources and expertise of the Group in designing studies which identify psychosocial problems, select the appropriate instruments for measuring their magnitude and frequency, and when possible, test interventions that will overcome the problems.
2. To study the effectiveness of psychotropic medication for treating identified psychological and somatic syndromes.

Accomplishments:

Psychological Responses of Cancer Patients to Informed Consent Procedures and Treatment by Investigational Chemotherapy protocol developed by the Drs. Holland, Penman, and Bahna completed with 118 subjects entered from all three investigative units. Initial trust in the doctor was cited most frequently as a major reason patients accepted treatment in investigational chemotherapy trials. Information about treatment is retained better when imparted by the doctor than information presented in written form; even so, much of the information learned is forgotten within one to three weeks.

Prevalence of Clinical Levels of Psychiatry Disorder in an Oncology Population protocol by Dr. Derogatis completed data collection at the end of March 1981. One hundred seventy-two cancer patients in treatment randomly selected from hospital and ambulatory settings at three institutions provide data base. This prevalence study represents the first attempt to establish psychiatric prevalence data for cancer patients. This information will be important for the antidepressant drug trial study to follow.

The Efficacy of a Tricyclic Antidepressant in the Treatment of Pain Among Cancer Patients protocol is planned by Dr. Holland as a parallel study to the above study of depression and is to run concurrent.

Pretreatment Crisis Period Coping protocol proposed by Dr. Schmale remains in draft form and is undergoing pilot testing by the Rochester Unit. It is a combined prevalence and predictive study of coping strategies and coping effectiveness pre first treatment for post treatment (three-six months later) somatic and psychological well being.

Plans: During the current grant year we will collect data on the depression and pain protocols, make decisions about implementing the coping protocol and prepare for follow-up studies in areas where further data is needed. Activities also include reviewing goals and establishing priorities for continuing our collaborative research in a competing continuation proposal to be submitted to NCI by June 1, 1981.

Program Director: Jan Howard, Ph.D.

Publications:

Morrow, G., Feldstein, M., Adler, L.M., Derogatis, L.R., Enelow, A.J., Gates, C., Holland, J.C., Melisaritos, N., Murawski, B., Penman, D., Schmale, A., Schmitt, M., Morse, I.: Development of brief measures of psychosocial adjustment to medical illness applied to cancer patients. Gen. Hosp. Psych. 3 (2), in press.

Grant 19744: Binding of N-Nitroso Carcinogens to Pancreatic Tissue

From 07/01/77 to 04/30/83

FY 81: \$102,452

Dr. Paul V. Woolley, Division of Medical Oncology, Georgetown University
Medical Center, 3800 Reservoir Road, Washington, D.C. 20007

Objectives: This study seeks to develop information regarding uptake and binding of N-nitroso compounds in the pancreas. This is of importance because several of the compounds have been demonstrated to be carcinogenic in animal models such as the guinea pig. Specifically, we wish to compare compounds that are known carcinogens with others that are not known carcinogens in the pancreas to see if they differ tissue levels or intracellular binding. Furthermore, we wish to examine whether compounds such as ascorbic acid, alpha-tocopherol or polyamines can alter or diminish the binding that is observed. The project seeks to develop comprehensive information regarding carcinogen levels, sites of binding and possible methods of diminishing tissue damages by compounds of this type.

Accomplishments: The past several months have been occupied by completing study on the levels of 1-methyl-1-nitrosourea (MNU) achieved in the pancreas of the guinea pig after oral administration. This copies the model of oral administration of MNU to produce pancreatic cancer in the guinea pig. It seems that MNU produces higher levels of drug in the pancreas after oral administration than does 1-methyl-3-nitro-1-nitrosoquandine (MNNG), the latter compound not being a recognized pancreatic carcinogen. We have found this relationship to hold in examining tissue levels of whole radioactivity, acid-precipitable radioactivity, or binding to DNA, RNA and protein. In each case, labelling by MNU was 2-30 times higher than that by MNNG. Next to the liver, highest tissue levels of MNU were found in pancreas and kidney following oral administration. Other tissues had lower levels. We are confirming this by examining formation of 7-methylguanine and O⁶ methylguanine in these tissues. We have also examined in some detail the uptake and binding of the compound 1-ethyl-1-nitrosourea (ENU) in the pancreas and other organs, and are in the process of making a specific comparison of this drug to MNU and MNNG. As with the first two drugs, we have seen modification of nuclear proteins by ENU, with histone H1 a primary target, as well as H4 and other histone proteins as well. In the next few weeks we hope to initiate studies with the very specific carcinogen N-nitroso-N-(2-hydroxypropyl)-N-(2-oxopropyl)amine and to compare that with MNU and the other compounds that we have examined to date.

Plans: The plans of this project remain to compare the two pancreatic carcinogens MNU and HPOP to other N-nitroso compounds and to each other in terms of the amount and type of pancreatic damage that they cause in the guinea pig. It is hoped that from this we will develop not only important understanding of the interactions of these compounds with the pancreas, but also methods of modifying the interactions.

Program Director: William E. Straile, Ph.D.

Publications:

Pinsky, S., Lee, K. and Woolley, P.V.: Uptake and Binding of 1-Methyl-1-Nitrosourea (MNU) and 1-Methyl-3-nitro-1-nitrosoquanidine (MNNG) by the Isolated Guinea Pig Pancreas. Carcinogenesis, 1:567-575 (1980)

Woolley, P. V. and Pinsky, S. D.: Binding of Nitrosocarcinogens in Pancreatic Tissue. Cancer 47:1485-1489 (1981)

Woolley, P. V. and Yerino, P.: Distribution and Binding of the Carcinogens 1-Methyl-1-nitrosourea (MNU) and 1-Methyl-3-nitro-1-nitrosoquanidine (MNNG) After Oral Administration in the Guinea Pig. Proc. Am. Assoc. Can. Res. 22:86 (1981)

From 07/01/80 to 06/31/82

FY 81: \$124,634

Ruth M. Heyn, M.D., University of Michigan Medical Center
Ann Arbor, Michigan 48109

Objectives. The major objective of the Clinical Cancer Education Program at the University of Michigan was to improve the multidisciplinary instruction in cancer at all levels. This included continuing curricular review of the medical student program; support of selected research projects for medical students in fields related to biochemistry or immunology of cancer at a basic level; support of clinical associates in medical, gynecologic, and pediatric oncology who function as junior faculty for an array of medical students and residents; partial support of junior faculty in medical, pediatric and surgical oncology to allow major teaching commitments to be accomplished in these areas; and organization of postgraduate courses for practicing physicians. Several videotapes on myeloproliferative disorders were planned for house officer and/or practicing physician use.

Accomplishments: The twenty-hour sophomore core curriculum in cancer underwent additional minor revisions and was coordinated by the associate program director as part of the Introduction to Clinical Health Sciences. Seven freshmen and two sophomore medical students received support while working in basic research laboratories of the biochemistry, immunology, physiology and anatomy departments. Three abstracts have been submitted by these students for presentation. Two clinical associates in gynecologic oncology, three in medical oncology and one in pediatric oncology were supported. These physicians had a major and continuing impact on instruction of junior and senior medical students and residents, and on maintaining interdisciplinary tumor conferences in their departments. A junior faculty member in pediatrics, in medical oncology and in surgical oncology each received partial support which resulted in major teaching efforts at the junior and senior medical student and resident level. The pediatric faculty member was given the annual award for excellence in teaching by the pediatric house officers. A videotape and two slide-tape programs on non-Hodgkin's lymphoma and chronic lymphocytic leukemia were competed, and an evaluation of two earlier videotapes accomplished. A postgraduate course in clinical oncology was organized and given, and a research seminar on "Innovative Approaches to Cancer Pharmacology" included a visiting professor supported by the grant. Travel monies allowed the clinical associates to either take selected postgraduate courses in their fields or to attend one national oncology meeting.

Plans: Continued support will allow extended teaching efforts to be directed at every level of medical student and resident training by the clinical associates and faculty. It will allow the early exposure of medical students to research laboratory activities addressing problems of growth and neoplasia. Enrichment of the program by visiting professors, and by courses and meetings outside the University will be possible.

Program Director: Margaret H. Edwards, M.D.

Grant 19764: Human Radiation Carcinogenesis Study

From 8/1/80 to 7/31/83

FY 81: \$135,820 (estimated)

Elizabeth D. Woodard, M.D., M.P.H., University of Rochester
Rochester, New York 14642

Objectives: Although much has been learned from animal experimentation about the mechanisms of radiation carcinogenesis, quantitative data on the risks of exposure of man can only be obtained from epidemiological studies of irradiated populations exposed to known doses of ionizing radiation. Continued surveillance of these irradiated populations, already followed for more than 25 years, will provide data on which to base predictions of the risks of radiation-induced disease. They are unusual in that the radiation exposure was of a therapeutic nature, so that radiation doses are known. Treatments were given for benign conditions which have not been identified as confounding variables in the subsequent development of neoplasia. The size of the populations and the period of follow-up are such that the effects of prior radiation exposure are evident and have reached a level of statistical significance.

Accomplishments: By the completion of this fiscal year, analysis of the data from the fifth survey of 2,863 thymus-irradiated persons and their 5,083 sibling controls will be completed. Additional dosimetry calculations for breast tissue in the thymus series will allow analysis of dose-response relationships for this tissue as well as for the thyroid gland. The fourth survey of the series irradiated for lymphoid hyperplasia of the nasopharynx (965 x-ray treated and 416 radium treated) and their 2,725 sibling controls has been initiated. A report describing the results of the third survey has been submitted for publication. The x-irradiated subjects in the LHNP series were found to have a two-fold increased incidence of tumors of the head and neck. For radium-treated subjects, the data suggested an increased risk of neoplasia involving the salivary glands and brain. Dosimetry calculations are being performed in this series for thyroid, pituitary and salivary glands for quantitative analysis of dose-response relationships. Coding of data from the fifth survey of the breast-irradiated series of 606 women and their controls (657 sisters; 539 women with mastitis not treated with x-rays and their 206 sisters) is nearly completed. The fourth screening by mammography and physical examination of the breasts of the irradiated and control women will be completed this fiscal year. A report describing results in the screening program has been submitted for publication. Records for each of the studies are being microfilmed to prevent loss of data.

Plans: (for the current fiscal year)

- (1) Initiate 4th survey of LHNP series
- (2) Submit for publication report of third survey of LHNP series and report of breast cancer screening program.
- (3) Conduct 4th breast cancer screening program for breast-irradiated series and sister controls.
- (4) Initiate analysis of data from fifth survey of breast irradiated series.

Program Director: Winfred F. Malone, Ph.D.

- (5) Complete analysis of data of fifth survey of thymus series and prepare report.
- (6) Microfilm all patient records.

Publications:

Shore, R., Woodard, E., Pasternack, B., and Hempelmann, L: Radiation and host factors in human thyroid tumors following thymus irradiation. Health Physics 38: 451-465, 1980.

Dvoretsky, P., Woodard, E., Bonfiglio, T., Hempelmann, L., and Morse, I.: The pathology of breast cancer in women irradiated for acute post-partum mastitis. Cancer 46: 2257-2262, 1980.

Woodard, E.: Neoplasms in irradiated human populations. Bureau of Radiological Health Symposium on Biological Effects, Imaging Techniques and Dosimetry of Ionizing Radiation, June 6/8, 1979, Rockville, Md. HHS Pub. (FDA) 80-8126, 1980, pp. 5-14.

Shore, R., Woodard, E., Hempelmann, L., and Pasternack, B.: Synergism between radiation and other risk factors for breast cancer. Preventive Medicine 9: 815-822, 1980.

Woodard, E.: Risk of thyroid cancer after irradiation in childhood. IN Cancer: Achievements, Challenges, and Prospects for the 1980's, Vol. I, (J. Burchenal and H. Oettegen, eds.), Grune and Stratton, New York, 1981, pp. 199-207.

From 07/01/76 to 06/30/84

FY 81: \$127,367

Dr. Robert C. Hickey, The University of Texas System
Cancer Center, M.D. Anderson Hospital and Tumor Institute,
Houston, Texas 77030

Objectives: The objectives of the Clinical Cancer Education program are to develop a cadre of physicians with the interest, background, capability, and resources (1) to conduct effective and progressive cancer education programs, and (2) to deliver the foremost techniques of cancer patient care in our institution and other institutions throughout the country.

To bring about these objectives, our educational programs have been made available to trainees at an earlier level in their educational experience, and educational opportunities have been expanded where need has existed. Increased mechanisms have been employed to insure comprehension, and new instructional aids have been produced and evaluated.

Accomplishments: The following have been planned and implemented to achieve these goals:

1. Clinical Oncology Grand Rounds. Held each Friday, these one-hour lectures concentrate on clinical diagnosis and treatment of the major neoplastic diseases.
2. Research Seminars in Basic Science. The 37-week series of one-hour seminars presents new developments in the basic sciences that apply to research on the mechanisms of action and potential cure of neoplastic diseases.
3. Fundamentals of Oncology: I. Special Topics in Basic Science; Fundamentals of Oncology: II. Application of Basic Science to Clinical Research. These two courses, to be taken in sequence, are offered to all fellows and residents, and are designed to supplement the basic science knowledge of the participants and to integrate their knowledge into clinical research. Each course lasts six months, with one and one-half hour meetings weekly.
4. Clinical Assistants/Dental Student Program. Dental fellowships have been established to provide eight four- to eight-week fellowships during the summer months to outstanding dental students.
5. Clinical Assistants/Medical Student Program. Undergraduate fellowships have been established to provide a broad elective educational experience in oncology and related fields. This experience is directed toward cancer as a clinical diagnostic and therapeutic problem, as a fundamental biological question, and as a sociological public health issue.
6. Clinical Associates/Faculty Associates. The individuals selected and funded by the program are knowledgeable in oncology, and bring to the program extensive experience in teaching nurses, medical students, interns,

Program Director: Margaret H. Edwards, M.D.

and residents. The program provides them further experience in the educational process and utilizes their experience, skills, and knowledge to educate others.

7. Professional Associates/Junior Faculty. Eight Professional associates have been provided partial support by the program to assist in curriculum design, organization, and evaluation of department and institutional cancer education programs.
8. Program evaluation. Administrative assistance is provided the program director and psychometrician for coordination of information requested by both the National Cancer Institute and this institution, and program evaluation procedures.

Plans: By combining the institutional clinical experience and clinical research education program with clinical science and basic science didactic education supported by both clinical and basic science departments, the Clinical Cancer Education program will continue to meet many of the immediate educational goals necessary for the well-balanced and complete education of students at the several levels of differentiation, and of clinicians and clinical researchers in the oncology subspecialties. To continue to achieve and to expand these goals, an increased responsibility will be undertaken in the undergraduate medical teaching program of The University of Texas Health Science Center Medical School at Houston.

From: 07/01/76 to 06/30/82

FY 81: \$122,028

Dr. R.W. Brockman, Southern Research Institute, 2000 Ninth Avenue South,
Birmingham, Alabama 35255

Objectives: Objectives of this study are the determination of biochemical effects of known and new anticancer agents, alone and in combination with other agents, on murine colon tumors in vivo, on host tissues, and on colon tumor cells grown in culture. Biochemical bases for use of inhibitors of purine biosynthesis and purine analogs, and alkylating agents alone and in combination have been or are under investigation. The selection and overgrowth of drug-resistant colon tumors was demonstrated to be a threat to successful experimental chemotherapy of colon cancer, as it is in the treatment of other cancers.

Accomplishments: We observed that 9- β -D-arabinofuranosyl-2-fluoroadenine (2-F-araA) was phosphorylated in colon tumor 36 in vivo to 2-F-araATP, which was shown to be an inhibitor of both ribonucleotide reductase and DNA polymerase. 2-F-araA was chemotherapeutically active against colon tumor 36 but not against arabinosylcytosine-resistant sublines, which were found to be deficient in deoxycytidine kinase activity.

Murine colon tumors differ in their response to therapy with nitrosoureas. Methyl CCNU was more effective against colon tumor 26 than it was against colon tumors 36 and 38. MeCCNU is more inhibitory to macromolecular synthesis, particularly DNA synthesis in colon tumor 26 in vivo, than it is against other tumors, even though similar quantities of [14 C] derived from [chloroethyl- 14 C] MeCCNU are associated with tumor DNA in all three tumors. Alterations in DNA sucrose-gradient sedimentation patterns and in extent of binding of ethidium to DNA from MeCCNU-treated 26 cells in culture suggest the occurrence of both strand scission and cross-linking. It was observed that murine colon tumors 26, 36, 38, and 41 are more responsive to treatment with 6-thioguanine (TG) than are 06A and 07A. The activity of hypoxanthine-guanine phosphoribosyltransferase, the enzyme that activates TG by converting it to the nucleotide, is not significantly different in these responsive and unresponsive tumors. Thus, the basis for differential activity lies elsewhere.

Plans: We are continuing our studies of biochemical effects of combinations of alkylating agents with analogs and enzyme inhibitors since certain combinations, nitrosoureas and thiopurines, have shown synergistic inhibition of experimental tumors. We also plan to study further the effects of 2-F-araA and other new agents in cultured colon tumors. We believe the development of better agents and combinations of agents for use against colon cancers refractory to chemotherapy to be essential.

Publications:

Brockman, R.W.: Resistance to Therapeutic Agents. In Cancer: Achievements, Challenges and Prospects for the 1980s, J.H. Burchenal and H.F. Oettgen, Eds. New York, Grune and Stratton, 1981; Vol. 2, pp. 55-66.

White, L., Shaddix, S.C., Cheng, Y-C., Brockman, R.W., and Bennett, L.L. Jr.: Inhibition of Ribonucleic Nucleotide Reductase and DNA Polymerases of Tumor Cells by 9- β -D-ARA Binofuranosyl-2-fluoroadenine 5'-Triphosphate (2-F-ara-ATP). Proc. Am. Assoc. Cancer Res., 22:33, 1981.

Program Director: Vincent J. Cairoli, Ph.D.

From 06/30/76 to 03/31/83

FY 81: \$631,015 est.

Dr. Jan W. Steiner, Illinois Cancer Council, 36 S. Wabash Avenue
Chicago, Illinois

Objective: The short-term objectives are: (1) to bring about a clear understanding of the functions and objectives of the Comprehensive Center by all relevant institutions in the State; (2) to develop an information system capable of providing a continuing, compatible and responsive data base to serve the participating institutions; (3) to develop a variety of interactive multidisciplinary and multi-institutional model networks in any or all of the research, education and patient management areas; (4) to conduct evaluative studies of the effectiveness of these models, setting the stage for extension or replication of successful models amongst different sets of institutions. Long-term objectives are: (1) to aim for a comprehensive, interactive multidisciplinary and multi-institutional system, utilizing partly common and partly shared resources for furthering education, research, and cancer-related health care in the Illinois area; (2) to serve as a model for the National Cancer Plan with capability to extend the operational template beyond the State of Illinois into adjacent or characteristically similar geographic areas.

Accomplishments: During this year, the Illinois Cancer Council's Cancer Control Programs will involve over 30 participating hospitals in Illinois. The projects underway and planned emphasize: (1) implementation and evaluation of cancer educational activities for health care professionals, and (2) research on new methods of evaluation of cancer control activities in terms of morbidity and mortality, new procedures for cancer patient care, and new techniques for delivering various services to cancer patients. A number of projects designed to describe and evaluate various systems for delivery of patient care in the community are being developed, including a community hospital oncology program, a pediatric outreach program, a randomized clinical trial comparing the impact of post-hospital discharge care of the ostomy patient by an enterostomal therapist versus a visiting nurse, and a demonstration of the impact of a master's trained oncology nurse as a resource to public health nurses and visiting nurses in two communities in Illinois. A project to distribute patient management guidelines in head and neck cancer, develop a scoring system for compliance to the Guidelines, and study physician compliance to them is being organized with the participation of 15 institutions. Three methods of guidelines distribution have been completed. Two methods of delivery of rehabilitation services to head and neck cancer patients, i.e., the multidisciplinary team approach and the dissociated approach, will be compared in another project including a continuing active program in cancer education for nurses, dentists, and speech pathologists; and planning for a multidisciplinary multi-institutional project to identify optimum methods of providing continuing education in cancer to health care professionals. This model educational program will address two topics in cancer care: clinical trials and prevention. Projects in new methods of cancer patient care include evaluation of new care of hearing problems re-

Program Director: Carlos E. Caban, Ph.D.

lated to treatment of head and neck cancer. A program to develop and implement multi-institutional protocols in patient care involving nurses and allied health professionals is underway with four such protocols under consideration.

Plans: Planning for a multi-institutional, multidisciplinary cancer prevention center is underway. Organizational meeting are scheduled in preparation for development of a number of projects, including the following: evaluation strategies for hospice services in Illinois, comparison of various cancer detection efforts in Illinois and their impact on patient morbidity and mortality, and establishment of a GOG cancer control program.

From 06/30/76 to 04/30/82

FY 81: \$68,883

Dr. Robert L. Goodale, Department of Surgery, University of Minnesota
Hospitals, 420 Delaware Street S.E., Minneapolis, Minnesota 55455

Objectives: The major aim of the project is to develop a sensitive method of endoscopic diagnosis for pancreatic cancer. Several aspects of endoscopy are under investigation. One is the development of a tiny flexible stainless steel microrasp to increase the yield of cytology at the time of ERCP. Another is the study of enzyme and nonenzyme protein in pure ductal aspirates from the pancreas to learn more about differences between pancreatitis and pancreatic cancer. We are correlating this data with a multiple regression analysis of clinical symptoms and signs. Also, we are continuing with tests of blood group antigens, to see whether such tests may be useful as a screening method.

Accomplishments: We have now studied in detail 139 patients with suspected pancreatic disease. Sixty had a confirmed pancreatic disease and a technically satisfactory ERCP study. In this group there were 23 with chronic alcoholic pancreatitis, 21 with confirmed cancer of the pancreas, and 16 with chronic pancreatitis of nonalcoholic origin. A staff radiologist, who was unaware of the correct diagnosis, reviewed all the films retrospectively, correctly identified chronic pancreatitis in 31 of 39 patients (80%), and correctly diagnosed pancreatic cancer in 79%. Cytology was positive in 54% of patients with cancer.

Multiple regression analysis of clinical findings was less accurate. It indicated that the most important clinical variable was jaundice followed by weight loss, smoking, age, and serum albumin, in order of decreasing importance. The sensitivity of this test was best for patients with nonalcoholic pancreatitis (81%) but was less for both alcoholic pancreatitis and cancer, with sensitivities around 70%.

Pancreatic juice analysis showed a paucity of zymogen patterns from the pH range of 6.5 to 9 in all three groups of patients. No identifiable pattern was unique to cancer. However, serum proteins could be detected in the pancreatic juice. There was significantly greater albumin concentration in pancreatic cancer than in either of the other groups or control patients, and a significantly greater IgG concentration and IgA concentration as well. The ratio of albumin to IgG in pancreatic fluid showed interesting differences. This study should encourage further study of nonenzyme serum proteins in the pancreatic juice. We believe that activation of a local immunoglobulin system in the pancreas may be involved in cancer.

Plans: We plan to study subfractions of immunoglobulins and albumins to see if they may be useful tumor markers.

Publications:

Goodale, R.L., Gajl-Peczalska, K., Dressel, T.D., Samuelson, J.: Cytologic studies for the diagnosis of pancreatic cancer. Cancer 47:1652-1655, 1981.

Program Director: William E. Straile, Ph.D.

Goodale, R.L., Dressel, T.D.: Experiences with pancreatic ductograms and pancreatic duct cytology. Symposia Specialists, 303-313, 1980.

Dressel, T.D., Goodale, R.L., Borner, J.W., Etani, S.: A study of the cholinesterases of the canine pancreatic sphincters and the relationship between reduced butyrylcholinesterase activity and pancreatic ductal hypertension. Ann Surg, 192:614-619, 1980.

Goodale, R.L., Condie, R.M., Gajl-Peczalska, K., et al. Clinical and secretory differences in pancreatic cancer and chronic pancreatitis. Ann Surg, in press.

Grant 20116: Cellular, Functional Analysis of Pancreatic Carcinogenesis

From 06/30/76 to 04/30/82

FY 81: \$68,219

Dr. H. Shinozuka, Department of Pathology, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania 15261

Objectives: The overall objective of the proposed study is to characterize the nature of the preneoplastic and neoplastic population of cells in the pancreas of experimental animals during chemical carcinogenesis at the cellular and functional levels, and to analyze mechanisms of evolution of pancreatic cancers. Studies by several investigators during the past years firmly established an experimental rat model in which a single or multiple injections of 4 hydroxyaminoquinoline-1-oxide (HAQO) or azaserine induce atypical acinar cell nodules (AACN), presumptive preneoplastic foci of acinar cell carcinomas. The major goal of the project is to clarify the histogenesis and biological behavior of AACN and cancer cells of the pancreas.

Accomplishments: We demonstrated that atypical acinar cell nodules (AACN) induced by azaserine are resistant to the necrogenic effects of cytotoxic agents, such as ethionine or 4 hydroxyaminoquinoline-1-oxide. This property acquired by the preneoplastic nodules of the pancreas in the early stage of carcinogenesis is quite analogous to the presumptive preneoplastic foci appearing in the liver of carcinogen-treated rats. It is possible that the evolution of AACN is the consequence of an initiation of acinar cells by a carcinogen and subsequent selection (promotion) of initiated cells to presumptive preneoplastic foci.

Cell cultures of pancreatic acinar cells originally obtained by collagenase dissociation of the pancreas of a Wistar rat, and several cell lines from the azaserine induced carcinomas were established and maintained. Both cancer cells and normal cells in culture contained small amounts of trypsinogen and chymotrypsinogen that could be detected by biochemical analysis and immunofluorescent stainings with antichymotrypsinogen. While cells derived from a normal rat at the 10-15th passage generation failed to grow as tumor when inoculated into nude mice, the cells after the 25th subpassages began to grow as tumors. Cancer cells contained elevated levels of total glycoproteins and a unique 51,000 dalton component not shared by the normal pancreas or other host tissues. Cancer cells also contained increased free fatty acids, free cholesterol and cholesterol esters.

Plans: We will continue to pursue the comparative studies of pancreatic acinar cell carcinoma in vivo and in vitro. In in vivo studies, we will continue to investigate the mechanism of tumor initiation and promotion in pancreatic carcinogenesis using azaserine-induced AACN as an experimental model. Dietary phenobarbital, amobarbital and pentobarbital will be tested to determine whether these agents exert efficient promoting activities in evolution of AACN. If results of our in vivo study on the pancreas warrant, effects of dietary barbiturates on cell proliferation of pancreatic acinar cells and cells in AACN will be initiated.

In in vitro studies, further characterization of a putative pancreatic acinar cell carcinoma-associated antigen, a 51,000 dalton glycoprotein,

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which we demonstrate in the transplantable tumors on nude mice, will be continued. Major emphasis will be placed on isolation of sufficient amounts of glycoprotein to ensure the antibody production in rabbits, and to determine cellular distribution of this glycoprotein. We will investigate the inter-relationship between glycoprotein and cholesterol metabolism in cancer cells (AT3A) with the use of specific inhibitors of glycoprotein (tunicamycin), and cholesterol metabolism (compactin).

Publications:

Rao, K.N., Takahashi, S. and Shinozuka, H.: Acinar cell carcinoma of the rat pancreas grown in cell culture and nude mice. Cancer Res. 40:592-597, 1980.

Rao, K.N., Misra, D.N., Kelly, R.H. and Shinozuka, H. Alterations in glycoproteins and lipids in azaserine induced acinar cell carcinoma. Cancer letters 10:19-26, 1980.

Shinozuka, H., Kelly, R.H., Misra, D.N. and Rao, K.N.: Studies on pancreatic acinar cells in culture. In Biology of Normal and Cancerous Exocrine Pancreatic Cells. Ed. Ribet, A., Pradayrol, L. and Susini, C., pp. 311-316. Elsevier/North-Holland Biomedical Press, 1980.

Grant 20198: Multidisciplinary Approaches to Pancreatic Cancer

From 09/15/77 to 05/31/83

FY 81: \$110,065

Dr. Parvis Pour (currently on leave), Acting Principal Investigator -
Dr. Terence Lawson, Eppley Institute for Research in Cancer and Allied
Diseases, University of Nebraska Medical Center, 42nd and Dewey Avenue,
Omaha, Nebraska 68105

Objectives: This investigation deals with the experimental induction of pancreas ductular cell tumors in hamsters with N-nitrosobis(2-oxopropyl) amine (BOP). The carcinogenicity of BOP is being examined in terms of its metabolism in vivo and in vitro, its ability to alkylate DNA in the target and non-target tissues and the ability of these tissues to repair any DNA damage produced by this alkylation. A further aspect of the study deals with a comparison of the hamster tumor and the spontaneous tumors which occur in humans.

Accomplishments: Metabolism: The metabolism of BOP has been studied in vivo and in vitro. In vivo, after a single dose of BOP (10 mg/kg; s.c.), a higher concentration of BOP and many of its metabolites was found in the pancreas than in the liver or salivary gland. At this dose, BOP is only a pancreas carcinogen. The other significant feature of this study was that N-nitroso-methyl (2-oxopropyl) amine (MOP) was formed in higher concentrations in the pancreas. MOP is believed to be a more proximate carcinogenic form of BOP. The in vitro metabolism of BOP was studied by incubating BOP (at various concentrations) with the microsomal fraction from hamster pancreas and liver. Both fractions metabolized BOP, but the pancreas microsomes produced more BOP than the liver. It is felt that these two aspects of BOP metabolism, i.e., the apparently greater concentrations of BOP and its metabolites which were formed in the pancreas and the apparently greater ability of the pancreas microsomes to metabolize BOP to more carcinogenic forms, are a strong indication of areas for future research.

Alkylation: The alkylation of hamster pancreas and liver DNA was studied using ($1-^{14}C$) and (2, 3- ^{14}C) BOP. It was found that the predominant form of alkylation in the pancreas was methylation whereas in the liver methylation and a form of three carbon alkylation also occurred.

DNA damage and repair: The extent of DNA damage and its repair was examined in hamster pancreas, liver and salivary gland after single doses of BOP (10, 20 or 40 mg/kg; s.c.). DNA damage was measured by alkaline sucrose gradient centrifugation of isolated nuclei. After a single dose of BOP (10 mg/kg), extensive DNA damage was observed in the three tissues, but it was repaired slowest in the pancreas (the target tissue for this dose). With the higher doses of BOP the damage persisted in the pancreas for as long as six weeks whereas only with a dose of mg/kg was DNA damage seen in the liver at four or six weeks.

Plans: We propose to exploit the tissue and species specificity of the carcinogenicity of BOP in hamsters and rats in an attempt to determine the mode of action of BOP by measuring the parameters outlined above. Allying this with what appears to be a specific phenomenon of the pancreas, i.e., its ability to concentrate this type of nitrosamine in

Program Director: William E. Straile, Ph.D.

the pancreas, we believe that we can determine much about not only the mode of induction of experimental pancreas cancer but nitrosamine carcinogenesis in general.

Publications:

Gingell, R., Brunk, G., Nagel, D., Wallcave, L., Walker, B. and Pour, P.: Metabolism and mutagenicity of N-nitroso-2-methoxy-2, 6-dimethylmorpholine in hamsters. J. Natl. Cancer Inst. 64:157-161, 1980.

Helgeson, A.S., Pour, P., Lawson, T. and Grandjean, C.J.: Exocrine pancreatic secretion in the Syrian golden hamster mesocricetus auratus--II. Effect of secretin and pancreozymin. Comp. Biochem. Physiol. 66A:479-483, 1980.

Pour, P., Salmasi, S., Helgeson, S. and Stepan, K.: Induction of benign and malignant lip tumors in Syrian hamsters by topical application of N-nitrosobis(2-oxopropyl)amine and N-nitroso(2-hydroxypropyl)(2-oxopropyl amine. Cancer Lett. 10:163-167, 1980.

Pour, P., Gingell, R., Langenbach, R., Nagel, D., Grandjean, C., Lawson, T. and Salmasi, S.: Carcinogenicity of N-nitrosomethyl(2-oxopropyl)amine in Syrian hamsters. Cancer Res. 40:3583-3590, 1980.

Langenbach, R., Gingell, R., Kuszynski, C., Walker, B., Nagel, D. and Pour, P.: Mutagenic activities of oxidized derivatives of N-nitrosodipropylamine in the liver cell-mediated and Salmonella typhimurium assays. Cancer Res. 40:3463-3467, 1980.

Pour, P., Sayed, S.E. and Wolf, G.L.: Considerations on the incidence of pancreatic cancer. Cancer Lett. 10:151-154, 1980.

Runge, R.G. and Pour, P.: Blood group specificity of pancreatic tumor mucin. Cancer Lett. 10:351-357, 1980.

Pour, P., Wallcave, L., Nagel, D. and Salmasi, S.: Induction of local epidermal papillomas and carcinoma by selected nitrosamines. Cancer Lett. 10:365-373, 1980.

Lawson, T.A., Gingell, R., Nagel, D., Hines, L.A. and Ross, A.: Methylation of hamster DNA by the carcinogen N-nitrosobis(2-oxopropyl)amine. Cancer Lett. 11:251-255.

Helgeson, A.S., Pour, P., Lawson, T. and Grandjean, C.J.: Exocrine pancreatic secretion in the Syrian golden hamster. I. Basic values. Comparative Biochem. and Physiol. 66A:473-478, 1980.

Pour, P.: Experimental Pancreatic Cancer, In "Pancreas Cancer" Edited by Moosa; Williams and Wilkins, Baltimore/London, 1980.

Grant 20222: Pancreatic Secretory Proteins in Cancer of the Pancreas

From 06/30/76 to 12/31/82

FY 81: \$31,658

Dr. H. Rinderknecht, VA Medical Center, Sepulveda, California 91343

University of California Los Angeles, 405 Hilgard Avenue, Los Angeles,
California 90024

Objectives: The objective of this study is to investigate changes of secretory proteins in pancreatic juice of patients with cancer of the pancreas which might yield basic information regarding the effect of a growing tumor on the secretory function of this organ and in turn provide clues to the early detection of this malignancy. Because of extreme difficulties in obtaining complete secretory profiles from such patients, a parallel study will be carried out with hamsters; pancreatic secretions will be analyzed before and periodically during induction of pancreatic tumors with bis-oxopropyl nitrosamine. Determinations of protein and about 10 digestive and lysosomal enzymes will be correlated with histological examination of the pancreas and are expected to furnish results potentially useful in early diagnosis of pancreatic tumors.

Accomplishments: During this year pancreatic secretory profiles from four patients with cancer of the pancreas have been obtained and cannulation of the pancreatic duct in a greater number of patients with suspected cancer of the pancreas has been carried out. High concentrations of certain lysosomal enzymes have been observed in the pancreatic secretions of some patients, but the variability of location and stage of the disease has precluded any consistent or specific finding solely attributable to the presence of a tumor.

Methods for determination of the digestive and lysosomal enzymes in pancreatic secretions of hamsters and a protocol monitoring the dynamics of secretion have been developed. Pancreatic juice from about 40 hamsters has been analyzed and baseline profiles for 10 secretory parameters established. An exploratory series of 90 carcinogen-treated animals is being investigated at present and followed for another six to nine months.

Plans: The study of pancreatic secretions in patients with cancer of the pancreas will be continued. Comparison of secretory profiles from normal and tumor bearing hamsters will be directed toward developing correlations between biochemical and histological abnormalities during development of tumors which might facilitate early detection of the disease. Additional secretory components will be monitored in future series of hamsters treated with carcinogen and a method will be developed for measuring plasma trypsinogen during carcinogenesis.

Publications:

Rinderknecht, H., Renner, I.G.: Increased cathepsin B activity in pancreatic juice from a patient with pancreatic cancer. New Eng J Med. 303:462, 1980.

Program Director: William E. Straile, Ph.D.

Grant 20226: Hormone and Carcinogen Effects on Prostate In Vitro

From 06/30/76 to 06/30/81

FY 81: \$0 (Ann. \$28,900)

Dr. Charity Waymouth, Interim Director, The Jackson Laboratory, Bar Harbor, Maine 04609

Objectives: (1) To select one or a few strains of mouse for experimentation in vitro.

(2) To examine aging mice for primary tumors.

(3) To devise optimal methods for preparing mouse prostatic cells for culture, for selecting the functional epithelium, and for securing cell-substrate attachment.

(4) To differentiate histochemically (acid and alkaline Phosphatase), in the cultures, acinar from stromal cells.

(5) To propagate normal mouse prostatic epithelial cells in a serum-free medium containing appropriate hormone, growth factor and other supplements, and to optimize the physical environment, e.g. pH and osmolality.

(6) To use the model to study the effects of carcinogens on cells that rarely become neoplastic in vivo.

Accomplishments: Objectives (1) through (4) have been major targets in the project in previous years. Objective (6) was not attained. During October 1, 1980 to the present, we have focussed upon conditions for culture of acinar cells from the dorsal and ventral lobes of BALB/cByJ mouse prostate. Our basic medium contains innovative features, e.g. the use of a non-bicarbonate (sodium beta-glycerophosphate) buffer system, which avoids the necessity to control $\text{NaHCO}_3\text{-CO}_2$ balance. Preparation of cells for culture includes disaggregation with collagenase. Attachment is improved by coating the culture surface with collagen or fibronectin. Selection against fibroblasts is either by use of a D-valine-containing medium or by inclusion of Gentamicin (and avoidance of Penicillin) or both. Hormones that improve the survival and growth of the acinar cells, and that are regularly included in the medium are: insulin, hydrocortisone, dihydrotestosterone and prolactin. In the presence of these no additional improvement in growth or viability was achieved with any of the following: mouse or ovine pituitary extracts, growth hormone, epiandrosterone, androstenedione or triiodothyronine at wide ranges of concentration. Among growth factors tested, Epidermal Growth Factor (EGF) was applied at 0.5 to 40 ng per ml and was most effective at 5.0 ng per ml. Bovine serum growth factor, and Fibroblast Growth Factor, were ineffective. Other factors that have improved the culture conditions include spermine, and transferrin. Our media contain a mixture of trace elements. As may have been predicted, raising the zinc concentration (from insulin and zinc sulfate) for prostatic cells by ten-fold (from 0.944 M to 1.885 M) is beneficial. Inclusion of selenium ($\text{Na}_2\text{SeO}_3 \cdot 5\text{H}_2\text{O}$ at 2.63 ng per ml) enhanced cell growth. Although established lines of mouse prostatic epithelial cells have not been achieved, cultures have been maintained in good condition without hyperplasia for up to 230 days. Cultures initiated in media supplemented with 5% fetal bovine serum have been compared with those maintained throughout in

Program Director: Andrew Chiarodo, Ph.D.

the defined media containing an array of supplements. The results suggest that all of the beneficial supplements have not yet been identified. The optimal pH appears to be 7.1 to 7.2, and osmolalities between 300 and 360 mOsm/kg support good cultures of prostatic epithelium.

Plans: Because of the impending partial retirement of the Principal Investigator, laboratory work will terminate in May 1981, and the remainder of the time on the grant devoted to writing. During the period 1 May 1980 to 1 July 1981, the P.I. will have been acting as interim Director of the Jackson Laboratory, an activity which has delayed the opportunity to prepare manuscripts for publication.

Publications: As noted above, no publications have yet been completed, except for a book chapter, as noted below, which refers (pp. 48-50) to this work.

Waymouth, C.: Studies on Chemically Defined Media and Nutritional Requirements of Cultures of Epithelial Cells. H. Katsuta (Ed.) Nutritional Requirements of Cultured Cells. Baltimore, University Park Press, 1978. pp. 29-61.

Grant CA 20322: Exploratory Studies for a Statewide Cancer Network

From 06/01/77 to 05/31/81

FY 81: 0 (Ann. \$304,471)

Dr. Phillip T. Waalkes, Comprehensive Cancer Center, Johns Hopkins Hospital, 600 North Wolfe Street Baltimore, Maryland 21205

Objectives: The primary objective of this Grant is to develop a regional Cancer Care and Control Network throughout the State of Maryland to involve key regional hospitals, appropriate community and state organizations, and individuals. The goals of this grant are: (1) to develop relationships and programs with these regional hospitals, their physician and nursing staffs, in order to establish the means whereby any patient with cancer can receive optimal clinical treatment under the best possible personal and essential management circumstances; (2) to work within these communities to determine and to assist in the development of priority cancer control interventions, programs and projects in accord with documented needs; and (3) to establish the essential data base for eventual total program evaluation.

Accomplishments: The activities involved in the consideration and planning of a regional Cancer Network in Maryland were only attempted after careful review and deliberations by the Oncology Center's Cancer Control Directorate and by its core faculty and staff as to the potential value of the Network for implementation of Cancer Control Programs. A detailed resource study was carried out to determine key regional hospitals, resources from multidisciplinary patient management, existing cancer control efforts and patient referral patterns in Maryland. A subsequent plan of approach was devised to be carried out initially in four discrete regions in the State and which involved three related though separate activities: (1) under the direction of Dr. Paul White, a Community Organization and Reconnaissance Program was initiated. Through this Program a clear picture as to important health related organizations and individuals in each region was gained. Interrelationships, attitudes, and mechanisms were studied and determined whereby decisions as to implementation of health programs were made; (2) under the direction of Professor Sam Shapiro, (a) Public, (b) Provider, and (c) Patient Surveys were conducted in order to aid in the establishment of needs and priorities for specific cancer control programs and to develop baseline data to be used for evaluation purposes; and (3) under the direction of Dr. Waalkes, steps were taken to involve key regional Community Hospitals of vital importance to the four areas of initial study. Because the Network was conceived as eventually Statewide, essential hospitals to the Network organization in other areas of the State were also considered. For a multidisciplinary approach, for assuring adequate and uniform data collection for review and evaluation, and to develop an organization with which to interrelate in each hospital, emphasis has been placed on the American College of Surgeons program requiring: (a) a multidisciplinary committee; (b) a professional education program; (c) a clinical management audit system; and (d) a tumor registry. The Center has been and is in an excellent position to assist, particularly with the latter three of these requirements. To date, the four regions in Maryland have been studied and 12 Hospitals (representing over 50% of the cancer patients/year in Maryland) have

Program Director: Carlos E. Caban, Ph.D.

signed agreements to be part of the Network. Based on the data collected and needs reviewed, preliminary priority cancer control programs have been initiated in one regional area. These have been implemented through a Regional Coordinating area. These have been implemented through a Regional Coordinating Advisory Committee with individual Task Forces to implement each priority project. Additional initial efforts are underway in all three of the other areas particularly related to hospital cancer programs. Three of the twelve hospitals aligned in the Network have approved cancer programs. The remaining nine are now in the process of formation.

Plans: For the next year plans have been developed for the study of the Baltimore Metropolitan area. It is recognized that Baltimore presents a much more complex situation and requires a modification of current strategies. To date, five hospitals in the Baltimore area, in addition to the Johns Hopkins Hospital, are included as part of the Cancer Network. Additional efforts will be made toward completion of comprehensive cancer programs in the four study regions in Maryland and toward a detailed clinical care Network in Maryland.

Publications:

Aplasia and Infection Control: Information for Patients. Baltimore, 1980, 66 pp.

Your Chemotherapy Medications, Baltimore, 1979, 18 pp.

Your Child's Chemotherapy Medication, Baltimore, 1979, 15 pp.

Elwood, T.W., Waalkes, T.P., and Vaughan, W.P.: Development of a Comprehensive Cancer Control Program. In Raymond Carlaw, (Ed.) Health Education Prospectives of the 80's, Nine Case Studies. In press. 1981

Grant 20396: Rehabilitation of the Head and Neck Cancer Patient

From 08/01/78 to 07/31/81

FY 81: \$19,094

Dr. Martin C. Robson, University of Chicago, Pritzker School of Medicine
950 E. 59th Street, Chicago, Illinois 60637

Objectives: This investigation for the University of Chicago, Pritzker School of Medicine proposed to establish a systematic, integrated multidisciplinary team approach for the treatment and rehabilitation of head and neck cancer patients. The investigation proposed to study a) microvascular surgical reconstructions in experimental and clinical settings, b) retention of maxillofacial prosthetic devices for prosthetic rehabilitation of head and neck cancer patients, c) psycho-social rehabilitation of head and neck cancer patients, d) speech evaluation and speech therapy for head and neck cancer patients before and after surgery.

Accomplishments: During the period from August 1, 1980 to the present an additional 35 patients with head and neck cancer have been evaluated by the project team. Eleven of these patients were candidates for microvascular reconstruction of their cancer defects and were successfully reconstructed. Of these patients, three were seen with a defect which required both skeletal and soft tissue. These three were reconstructed with the latissimus dorsi musculocutaneous-osseous flap which had been designed and evaluated in our laboratory and previously reported.

The extension grant which was awarded was used to further evaluate the arterial and venous flow in the new composite soft tissue-bone flap. All of the animals were completed and it was shown that this flap could be used with a single microvascular anastomosis for each artery and vein.

The three patients who had this flap used to totally reconstruct the mandible and floor of mouth as well as external skin proceeded without difficulty. The flap proved to greatly shorten the hospital time and performed in a single operation the reconstruction which previously required from four to six operative procedures. With this background, the project team has decided that people with oral mandibular defects requiring composite reconstruction of soft and osseous tissue would routinely undergo this procedure in the future.

The implantable magnet study showed that there was minimal reaction around the magnets both in the short and long term histological evaluation. Therefore, the concept of using either magnets or staples appears to be a viable concept in newly revascularized bone. This is at distinct odds with previous results using standard bone grafts which were not revascularized.

At present, all patients who have been reconstructed with microvascular anastomosis during the project, which total fifteen, are being evaluated by the psycho-social group and the speech therapists. It appears from preliminary data that speech is greatly improved with the one-stage reconstruction by microvascular anastomosis and that the shortened hospitalization required by this procedure has aided in the psycho-social readjustment.

Program Director: Lawrence D. Burke

Publications:

Schlenker, J.D., Indresano, T., Raine, T., Meredith, S.C., and Robson, M.C.: A new free flap in the dog containing a vascularized rib graft: The latissimus dorsi myo-osteocutaneous flap. Journal of Surg. Res. 29:172, 1980.

Schlenker, J.D., and Reus, W.F.: Comparison of blood flow after ischemia in island flaps: Latissimus dorsi myocutaneous and groin flaps in the dog. Plast. & Reconstr. Surg. (IN PRESS)

Schlenker, J.D., Robson, M.C., and Parsons, R.W.: Methods and results of reconstruction with free flaps following resection of squamous cell carcinoma of the head and neck. Annals of Plast. Surg. (IN PRESS)

From 07/01/79 to 06/30/82 FY 81: \$119,259

Dr. Donald W. Weston, Michigan State University, College of Human Medicine
101 East Fee Hall, East Lansing, Michigan 48824

Objectives: This program is designed to: (1) augment and enlarge oncology content in the preclinical and clinical medical curriculum through development of new teaching materials, work projects, courses, seminars, and electives, and additions to regular course offerings and required clerkships, and (2) meet Continuing Medical Education needs in oncology of full-time and clinical faculty at Michigan State University and on six campuses.

Accomplishments: (1) Two classification schemes were developed to identify oncology content in the preclinical curriculum. (2) An oncology knowledge examination to assess graduating medical students was developed and administered to the 1981 class. (3) The regular clerkships were reviewed for oncology content, and two required seminars were constructed by Grand Rapids Campus faculty to remedy perceived omissions. These seminars can be added to any clinical curriculum. (4) Clinical oncology materials are being integrated in Physiology, Pathology and Gerontology. (5) Clinical Assistants have: (a) developed hospice electives in two communities, (b) developed patient teaching materials, (c) worked on cancer-related research projects, (d) helped develop patient information forms, (e) worked with cancer registry organizations, and (f) worked on new curriculum objectives in oncology for Family Practice rotation and development of curriculum for new electives. (6) There has been a significant expansion of the Oncology library which, through a sharing system, is available also to the College of Osteopathic Medicine, the School of Nursing and the Clinical Campuses. (7) In direct response to the impetus of the cancer grant, the clinical campuses have: (a) developed three new oncology electives in Kalamazoo and Marquette, (b) added five oncology seminars in Lansing, Grand Rapids, Kalamazoo and Flint, (c) increased the number of oncology lectures for students and residents in Lansing, Kalamazoo, and Flint, and (d) incorporated oncology-related courses in Medicine and Pediatric clerkships in Saginaw and Flint. (8) Grant-supported Continuing Medical Education activities in oncology include: (a) a survey of oncology education needs (GRCOP registry data) and interests (MSU questionnaire) of physicians to guide choice of programs, (b) 6 programs in the Cancer Symposium series on MSU campus, (c) conference speakers in Dowagiac on cancer infections and in Flint on CNS tumors, (d) a Breast Cancer Conference in Saginaw and a "Cancer Update" Conference in Marquette.

Plans: Further curriculum augmentation: (1) correlation of oncology materials with Radiology, Microbiology and Biochemistry, (2) lecture seminars on psychosocial aspects of cancer, (3) incorporation of 8 instructional modules on Cancer Prevention into the curriculum on campus and in the communities, (4) implementation of a day-long oncology conference on campus each quarter attended by Phase III students and clinical campus residents and faculty, (5) continued support of appropriate CME programs in oncology, identified by MSU and community surveys, and (6) continued data collection and assessment of the effects of new programs.

Program Director: Margaret H. Edwards, M.D.

From 07/01/77 to 06/30/82 FY 81: \$139,957
Dr. W.P.L. Myers, Memorial Sloan-Kettering Cancer Center
1275 York Avenue, New York, New York 10021

Objectives: The Clinical Cancer Education Program at Memorial Sloan-Kettering Cancer Center (MSKCC) has the following specific objectives: (1) to educate in a multi-disciplinary fashion Clinical Associates in the Disciplines of Surgical Oncology, Medical Oncology, Pediatric Oncology, Radiation Therapy, and Radiologic Physics; (2) to support undergraduate medical and dental students in non-curricular research and clinical enrichment experiences; (3) to foster improved teaching of cancer at Cornell University Medical College (CUMC) through improved integration of subject matter between departments and through the establishment of teaching objectives in oncology; (4) to provide for the dissemination of current information regarding cancer research and therapy to physicians and other allied health workers.

Accomplishments: (1) In the report year 14 Clinical Associates were supported, in part, by this grant: Surgical Oncology - 5, Medical Oncology - 4, Pediatric Oncology - 2, Radiation Therapy - 2, and Medical Physics - 1. (2) Coordination of summer student research opportunities at CUMC and MSKCC has been accomplished and medical students have been selected as a joint undertaking. (3) There were 62 medical student members of the Student Research Society at CUMC taking part in the summer (1980) programs and 14 carried out their programs at MSKCC; of these 14, 5 were supported by this grant carrying out research studies in the following areas: (a) Phase I and II chemotherapeutic studies; (b) Morphologic classification to childhood acute lymphoblastic leukemia; (c) Studies of pulmonary function in cancer patients; (d) Principles and techniques of oncologic surgery. In addition there were 3 other medical students supported by the grant (2 from CUMC, one from New York Medical College) who did studies involving nutrition and cancer, cardiac ultrasound, and pediatric oncology. (4) Objectives for the teaching of oncology to undergraduate medical students at CUMC have been written by the Program Director and furtherance of these objectives has been initiated through a Standing Committee on Oncology. (5) A 22-hour interdisciplinary course for first-year medical students at CUMC now, for the first time, has a 2-hour session on cancer developed by this grant's Program Director. (6) Electives at MSKCC in cancer and cancer-related subjects for medical students have been developed as follows: 9 electives for first year students, 10 for second year students, and 37 for fourth year students. In the report year 112 medical students from CUMC and 132 medical students from other schools took these electives. (7) In the report year 19 dental students from Howard University and Georgetown University received partial support from this grant for enrichment clinical electives (non-curricular) at MSKCC. (8) Thirty-two conferences and courses offering Category I credit in Continuing Medical Education (CME) were held during the report year. An additional 13 CME Category I activities were co-sponsored with other medical organizations and institutions.

Plans: During the fifth year of the current five-year award we plan to support Clinical Associates (at a reduced level - 9 instead of 14 - owing to budget cutbacks) in the same oncologic disciplines as noted above except possibly Radiologic Physics. The summer program for students and student electives will continue as will efforts to improve the teaching of cancer at CUMC. Evaluation of these programs will receive greater attention. An expansion of CME programs is also planned.

Program Director: Margaret H. Edwards, M.D.

Grant 20459: Prostatic Estrogen Receptor

From 06/30/76 to 04/30/82

FY 81: \$65,174

Dr. J. Edson Pontes, Medicine C, Roswell Park Memorial Institute, 666 Elm Street
Buffalo, New York 14263

Objective: The measurement of receptors in prostate cancers has been hampered by the unavailability of adequate biopsy material to be used with present methodology. Recently, a method developed by one of our investigators using high pressure liquid chromatography has the potential to measure estrogen receptors in small needle biopsy samples. This method has been validated using immature rat uteri with concomitant measurement done by standard techniques.

Accomplishments: The development of a micro method for the measurement of estrogen receptors has been accomplished in our laboratory. Prostatic specimens of 12 patients have been assayed and an additional 18 needle biopsies are presently being evaluated. Correlation between the presence of estrogen receptors and the clinical course of these patients is presently being done.

Plans: We intend to continue to evaluate needle biopsy specimens of prostatic carcinomas in an attempt to correlate the clinical course with the presence of estrogen receptors.

Publications:

A Micromethod for the Measurement of Estrogen Receptors Using High Pressure Liquid Chromatography. R. Y. Kirdani. J. Clin. Investigation. (Submitted)

Program Director: Andrew Chiarodo, Ph.D.

Grant 20615: Regional Development of Oncologic Social Work Skills Social Work
Oncology Group

From 01/01/78 to 12/31/80

FY 81: \$83,716

Marion F. Stonberg, Sidney Farber Cancer Institute, 44 Binney Street,
Boston, Massachusetts 02115

Objectives: The objective of this program is to improve the quality of life of cancer patients and their families. One method of achieving this goal is:

1. By upgrading the skills of social workers who work with cancer patients and their families through education.
2. By promoting cooperation and sharing information and expertise among social workers.
3. By offering peer support to social workers in a variety of settings providing services to these individuals.

Accomplishments: The following components of the program have continued: Monthly meetings at SFCl; 2300 copies of the SWOG-NEWS are distributed monthly. The course, Cancer and Social Work, was held in April and October. On October 4, the symposium "Cancer Dynamics" for students in all the schools of social work in New England was held. Symposia: June 5 and 6, a two day symposium, "The Impact of Social Work on Long Term Care," jointly sponsored by NASW Nursing Home Task Force and SWOG: October 17, one day "Support Groups for Cancer Patients and Families," jointly sponsored with the Massachusetts Division, ACS; November 20, one day "Bereavement."

Regional Meetings and Symposia: Region I - February 13, September 17, November 12; Region III - May 6; Region IV South - January 23, April 10, May 30, October 14; Region V - January 25, February 22, March 28, April 25, May 16, June 27, September 26, October 24, November 21; Region VI - February 27, May 6, September 23, November 18; Connecticut - February 25, March 27, May 29, October 29; Northern and Eastern Maine - February 8, October 28; Central and Southern Maine - February 25, March 27, October 29; Rhode Island - September 25, 1980.

On March 29th at the Fox Chase Cancer Center in Philadelphia, on April 17-18 at the Medical College of Wisconsin and the Milwaukee County General Hospital, and on October 1-4 at the American Association for Cancer Education Annual Meeting at the University of Louisville Cancer Center in Louisville, the Principal Investigator, Marion Stonberg was invited to present papers on "Social Work with Cancer Patients" and "SWOG." A Mid-Atlantic SWOG program is functioning out of the Fox Chase Cancer Center. This program was started with the advice and guidance of SWOG at SFCl. Other areas are in the planning stages and we are collaborating with them. The Central Resources including the reprints, library of books and videotapes is enlarging. We are now a resource for Biospherics, ACS, local educational institutions as well as newly developing SWOG programs.

Plans: Because the SWOG Continuation Grant was approved and not funded, the period of termination is being used to ensure that the program continues and develops

Program Director: Lawrence D. Burke

into a National Group. A two day National Conference is planned for July 2 and 3, 1981 in Pittsfield, Massachusetts. Individuals attending will be able to stay on for the July 4th weekend at Tanglewood. It is anticipated that since this conference has attracted a lot of interest nationwide that some new regional groups and ultimately a national group will evolve. Measures are being taken to ensure the continuation of the program.

Upcoming presentations include the keynote address and two workshops at the Fred Hutchinson Cancer Center on May 15, 1981 dealing with Oncology Social Work and the SWOG program presented by Marion Stonberg: also, on May 15, a presentation by the Foundation of Thanatology by Jan Braun, Co-Director for Regionalization of SWOG.

Grant 20643: Clinical Cancer Education Program

From 07/01/79 to 06/30/84 FY 81: \$80,163
Dr. John J. Costanzi, U.T. Galveston Cancer Center
U.T. Medical Branch, Galveston, Texas 77550

Objectives: The program is designed to provide an organized, multidisciplinary educational program for undergraduate medical students, house staff and postgraduate physicians, practicing physicians and other health personnel, patients, and the community. This will be accomplished through curricular analysis and enrichment in the schools of medicine, nursing, and allied health; the development of teaching materials for various learner groups; through continuing education of practitioners; through support of patient education, and through efforts to educate and inform the public.

Accomplishments: (1) Organized an educational staff to support UTMB cancer education efforts; (2) completed and published the review of cancer teaching in the undergraduate medical and nursing curriculae using the Tracer Method of Analysis; (3) developed instructional materials to enrich the curriculae including units on Breast Cancer, Nursing Care of the Adult Cancer Patient, and Principles of Oncology in Nursing; (4) increased the number of multidisciplinary clinical oncology teaching conferences, rounds, and lectures; (5) identified and published an annotated list of instructional materials available to augment education programs for the undergraduate, house staff, and postgraduates; (6) enhanced the quality of the Cancer Center Seminar Series by bringing in visiting professors with reputations for excellence in oncology; (7) trained five clinical associates in medical and radiation oncology; (8) completed continuing education programs for practitioners at several sites including El Paso, Austin, Denison, and Galveston; (9) developed patient education materials on, "How to Live with a Laryngectomy"; (10) developed a brochure describing elements of the cancer effort at UTMB; and (11) published a quarterly Newsletter, "Cancer Perspectives" as an educational resource for public and community education.

Plans: Future activities will focus on evaluation of the program of Clinical Cancer Education at UTMB and various special projects. A multidisciplinary oncology elective for the undergraduate medical curriculum, an analysis of cancer teaching in the allied health undergraduate curriculum, and continuation of the Cancer Center Seminar Series, Continuing Education of Practitioners, and training Clinical Associates are activities planned for subsequent years' efforts. The Cancer Center Education branch will continue to serve as a resource to the UTMB cancer education effort.

Program Director: Margaret H. Edwards, M.D.

From: 07/01/77 to 6/30/83 FY 81: \$71,317
Dr. James Lepley, Memorial Sloan-Kettering Cancer Center
1275 York Avenue, New York, New York 10021

Objectives: To train qualified prosthodontists in maxillofacial prosthetics; qualified prosthodontists are those who have attained board eligibility status by successful completion of a program in general prosthodontics approved by The American Dental Association's Council on Dental Education.

Accomplishments: Participation in New York College of Dentistry Cancer Enrichment Program; the entire senior class spends one half-day daily per week in various activities at Memorial Sloan-Kettering Cancer Center including Head-and-Neck clinic and Conference, Dental Service seminars, operating room (Head-and-Neck), Pathology, and Radiation Therapy clinics. The core curriculum is that of New York University graduate students in Prosthodontics on an elective basis, since all of program participants are from other programs which have supplied at least 50% of the necessary core study. Memorial Sloan-Kettering Cancer Center offers a cancer seminar series which is attended on an elective basis when deemed appropriate to prosthodontic training. There are two clinical associates whose activities are totally devoted to management of the problems of the Head-and-Neck cancer patient in supplying intra- and extra- oral prostheses and also the complexities of the management of various other modalities of cancer treatment such as radiation therapy, chemotherapy, immunotherapy, resulting in difficult and sometimes obscure treatment complications.

Research is both clinical and basic. Radiographic studies indicate a definite cessation of tooth bud development following radiation therapy to the maxilla and mandible in the tooth formative years. It is also suspected that certain chemotherapeutic agents may cause the same phenomenon. Clinical and laboratory research continues in use of elastic, compressible silicones for use in obturator bulb and endodontic pins. The latter is in the laboratory/clinical investigative phase at this time. Also, a proposed double-blind study relating to postoperative pain is being initiated incorporating the use of a steroid substance (prednisone) with local anesthetic with the perio-press injection technique following endodontic treatment. Analysis of patient history and follow-up data is being gathered relative to effective care relating to long term radiation therapy and chemotherapy.

Plans: Plans are being formulated to expand investigation into the following areas:

- (1) use of flexible silicones as implants since they are non-toxic to the tissue;
- (2) further compilation of reactivity of tooth buds to radiation therapy and chemotherapy;
- (3) continuation of endo post research since the salvaging of teeth, roots, etc., is vital to success of intraoral prostheses; and

Program Director: Margaret H. Edwards, M.D.

- (4) greater emphasis seems to be forthcoming on surgical rehabilitation by the Head-and-Neck surgeons; the third year clinical associates are heavily involved in providing exotic, sometimes bizarre fixation prostheses which they place during the operative procedure. This is being done under the direction of the Program Director and the Chief of the Head-and-Neck Service.

From 02/01/80 to 01/29/83.

FY 81: \$72,830

Dr. C. P. Morrow, University of Southern California, Los Angeles,
California 90007

Objectives: The primary objective of this project is to enhance the availability of quality care for women in the western United States with trophoblastic disease (TD) through the regional resource outreach program. A secondary objective is to utilize the clinical information, tissue specimens, and sera of patients with trophoblastic disease obtained through this regional outreach program (in addition to our large intramural trophoblastic service) for research directed toward improved diagnosis and treatment of this disease. Malignant trophoblastic disease (invasive mole, choriocarcinoma) complicates 20 percent of molar pregnancies. The management of high risk cases in specialized treatment institutions results in twice the remission rate achieved when management is carried out by the community physician. Dissemination of information through educational programs should improve the recognition of these cases. The clinical research described in this project has much potential to improve patient care.

Accomplishments: During the past year of this grant, the community physicians have continued to be served through provision of a reliable and sensitive hCG radioimmunoassay. Seven hundred and twenty assays have been done on approximately 130 new patients. The post-molar regression curve has continued to be analyzed as a guide to diagnosing trophoblastic neoplasia. In associated laboratory studies, an androgen-binding protein has been identified for the first time in molar and placental tissue.

Plans: Future plans include: evaluation of a free alpha hCG submit assay in the monitoring of trophoblastic disease; the analysis of tumor cytosols for hCG, free alpha and beta submits; comparison of post-molar serum hCG regression curves on patients using hormonal contraceptives with patients not using such contraceptives; and the organizing of continuing education courses on trophoblastic disease for community physicians.

Publications:

O'Brien, T.J., Engvall, E., Schlaerth, J.B., and Morrow, C.P.: Trophoblastic disease monitoring: evaluation of pregnancy - specific beta-1 glycoproteins. Am. J. Obstet. Gynecol. 138: 313, 1980.

O'Brien, T.J., and Morrow, C.P Antibody Fractionation for improved sensitivity and specificity of antisera to choriogonadotropin. Clin. Chem. 26: 1920, 1980.

Program Director: Robert T. Bowser, Ph.D.

Grant 20791: Simulated Breasts for the Training for Lump Detection

From 01/01/78 to 06/30/82

FY 81: 0 (Ann. \$175,895)

Dr. H. S. Pennypacker, University of Florida, Gainesville, Florida 32610

Objectives: The overall objective of this project is to determine, with the aid of accurate models of the human breast, the most efficient and effective method for training in the manual skills required for lump detection. Those variables relating to maintenance of the skill are being isolated so that a final training technology can be developed which will insure regular self-examination with predetermined proficiency.

Accomplishments: Biomaterials Engineering. A technology for producing high fidelity simulations of the human breast has been developed. Models can now be made to duplicate the natural firmness and nodularity of a given woman's own breast and movable lumps of varying size and hardness can be inserted to varying depths. Training Technology. A major study evaluated the effects of nodularity, lump hardness, lump depth, and movability on both detection threshold and proficiency. In general, these variables act as expected, but proficiency remains high even for medium sized lumps deeply embedded and surrounded by nodularity. Thus, the high fidelity model is usable as a training aid.

A second major study compared the effectiveness of training using (a) the woman's own tissue, (b) the model, (c) both together, or (d) the ACS pamphlet. Measures taken on the model before and after training revealed that the best performance resulted from training on the combination of the model and the woman's own tissue. Six month follow-up measures confirmed this result. A replication was conducted comparing conditions (b), (c), and (d) above using measures of BSE proficiency on the women's own tissue as the dependent variable. Again, the combination training is slightly superior to all others with pamphlet reading a distant third. Yet another investigation revealed that tape recorded instruction is little better than pamphlet reading.

Studies in progress include an investigation of controlled practice frequency in an effort to establish the maximum examination interval at which BSE proficiency can be maintained.

Plans: A large scale clinical trial of the fully developed BSE training technology has been proposed. A total of 8,000 women will be recruited and assigned to two groups - one to receive BSE training and the other to receive training at the current state-of-the-art level. A five-year follow-up will focus on number and size of tumors detected by the two groups.

Publications:

Hall, D. C., Adams, C. K., Stein, G. M., Stephenson, H. S., Goldstein, M. K., and Pennypacker, H. S.: Improved detection of human breast lesions following experimental training. Cancer, Volume 46, Number 2, July 15, 1980, pp. 408-414.

Program Director: Dorothy R. Brodie, M.D.

Whalley, C.E., Iqbal, Z.M. and Epstein, S. In Vivo and Microsomal Metabolism of the Pancreatic Carcinogen N-nitrosobis(2-oxopropyl)amine by the Syrian Golden Hamster. Cancer Research, 41:482-486, 1981.

The Centralized Cancer Patient Data System (CCPDS) Grants

Objectives: CCPDS is a standard system for registering persons with reportable malignant neoplasms, who are patients of Comprehensive Cancer Centers. Eligible patients were those first admitted to a center on or after July 1, 1977. All cases meeting certain requirements are reported to the Statistical Analysis and Quality Control Center (SAQC) in Seattle, Washington. SAQC is responsible for maintaining the system, analyzing the data and acting as the coordinator for research activities.

Thirty-eight items of information are collected on each patient, including demographic characteristics, diagnosis, therapy and survival. Standardized definitions of data items have been documented in the "CCPDS Data Acquisition Manual", (DAM). This manual also includes recommended procedures for abstracting, coding, submitting data to SAQC, and quality control.

Initially, standard definitions and codes were established for reportable patients and tumors, as well as for each of the 38 items. Criteria for quality control were set up to assess accuracy, completeness and timeliness of reporting. There is a continuing effort to maintain inter-center comparability and compatibility with other national and international cancer reporting systems. CCPDS data is disseminated according to policies and procedures developed by a Policy Advisory Committee for that purpose.

<u>Grant</u>	<u>Start</u>	<u>End</u>	<u>FY</u>	<u>Annual</u>	<u>PI/Organization</u>
21077	07/77	06/83	81	\$103,057	Richard B. Friedman, M.D./ University of Wisconsin
21169	09/77	08/83	81(est)	\$124,272	Roger Yurkco, M.P.H./ Memorial Hospital for Cancer and Allied Diseases
21182	07/77	06/83	81(est)	\$106,509	John R. Durant, M.D./ University of Alabama
21183	07/77	06/83	81(est)	\$142,497	Richard A. Cooper, M.D./ University of Pennsylvania
21184	06/77	05/83	81	\$152,223	William F. Taylor, M.D./ Mayo Foundation
21185	08/77	07/83	81(est)	\$ 65,862	Jack E. White, M.D./ Howard University
21186	06/77	05/83	81(est)	\$ 91,486	G. Burton Seibert, Ph.D./ University of Miami

Project Officer: Thomas C. Dundon

Whalley, C.E., Iqbal, Z.M. and Epstein, S. In Vivo and Microsomal Metabolism of the Pancreatic Carcinogen N-nitrosobis(2-oxopropyl)amine by the Syrian Golden Hamster. Cancer Research, 41:482-486, 1981.

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Project Officer: Thomas C. Dundon

<u>Grant</u>	<u>Start</u>	<u>End</u>	<u>FY</u>	<u>Annual</u>	<u>PI/Organization</u>
21188	06/77	05/83	81	\$ 98,592	Raymond E. Lenhard, Jr., M.D./ Johns Hopkins University
21190	06/77	05/83	81	\$140,473	Roger L. Priore, Ph.D./ New York State, Department of Health
21192	06/77	05/83	81(est)	\$ 96,800	Edwin B. Cox, M.D./ Duke University
21193	07/77	06/83	81(est)	\$112,621	Donovan J. Thompson, Ph.D./ Fred Hutchinson Cancer Center
21194	08/77	07/83	81	\$ 81,435	Diana B. Fisher, Ph.D./ Yale University
21751	07/77	06/83	81(est)	\$ 68,400	Martin D. Keller, M.D./ Ohio State University
21784	07/77	06/83	81(est)	\$ 81,221	Vincent F. Guinee, M.D./ University of Texas System Cancer Center
21898	09/77	07/84	81(est)	\$153,000	Richard B. Warnecke, Ph.D./ Illinois Cancer Council
23636	03/78	02/83	81	\$ 88,186	Robert M. Elashoff, Ph.D./ University of California at Los Angeles
24996	01/79	12/82	81	\$104,267	Alexander Walker, M.D./ Sidney Farber Cancer Institute
25146	03/79	02/82	81	\$ 41,663	Sidney J. Cutler, Ph.D./ Georgetown University
26921	05/80	04/83	81	\$174,123	Mary G. Curnen, M.D./ Columbia University
28295	05/80	04/83	81	\$122,820	Vainutes K. Vaitkevicius, M.D./ Michigan Cancer Foundation
31682	05/81	07/83	81(est)	\$112,563	Strother H. Walker, Ph.D./ University of Colorado

Accomplishments: These grants were originally funded in 1977. To date, twenty cancer centers have been funded. Approximately 50,000 new cases are registered each year at SAQC.

The CCPDS grants have resulted in a computerized patient data system in each of the centers. This system plus the quality control activities developed by SAQC have resulted in a higher quality, more efficient patient data system for the Center. In addition, these grants help support statistical activities within the Center which insure better research uses of the system.

Plans: The ultimate goal of CCPDS is to promote use of the system in carrying out cooperative research between centers. To date, approximately six studies are in reparation resulting from the use of the CCPDS.

Grant 21098: Clinical Cancer Education Grant

From 7/01/77 to 06/30/84 FY 81: \$63,711
Dr. Robert O. Greer, D.D.S., University of Colorado School of Dentistry
Denver, Colorado, 80262

Objectives: The objectives of the Clinical Cancer Education Grant at the University of Colorado School of Dentistry are threefold. The first objective is to enhance the diagnostic acumen of dental students, dental general practice residents, practicing dentists, faculty and associated health professionals as it relates to the detection of neoplasia of the head and neck. A second goal is to increase the management and therapeutic competency of all of the aforementioned in the realm of head and neck neoplasia. The third objective is to reinforce the concept of a team approach to the prevention, diagnosis, treatment and rehabilitation of the head and neck cancer patient.

Accomplishments: (1) Twenty-seven dental students rotated on oncology block assignments, fifteen third-year students and twelve fourth-year students. These block rotations included Tumor Board participation, Oral Pathology seminar, Head and Neck operating room, cancer research seminars, a literature review seminar and Radiation Oncology. (2) Five dental general practice residents rotated through the clinical cancer education program clinical series in an attempt to prepare them to recognize, analyze and appreciate primary and secondary oral disorders and neoplastic disease. Didactic instruction for residents included seminars on salivary gland tumors, common oral lesions, use of the clinical pathology laboratory, hematologic malignancies and oral epithelial tumors. (3) The Third Annual Oral Cancer Symposium was held in Aspen, Colorado on February 18-19, 1980. The Oral Cancer Symposium emphasizes current principles concerning oral cancer including diagnostic, therapeutic and rehabilitative parameters. (4) Salivary gland and pediatric tumor mini-courses were offered at the Annual Denver Midwinter Dental Meeting January 12-13, 1981. (5) A pediatric tumor course was offered to the Boulder County Dental Society on February 2, 1981. (6) The Colorado Oral Cancer Bulletin continues to be published semi-annually. It serves as an adjunctive educational aid to dentists, physicians, and associated health professionals in the area of cancer of the head and neck. (7) Dental hygiene students continue to participate in a four clock hours didactic presentation on the diagnosis and management of oral cancer. (8) A separate Head and Neck Tumor Board was developed as a multidisciplinary conference covering the aspects of prevention, detection, diagnosis, treatment and rehabilitation of the oral cancer patient.

Plans: (1) A Clinical Cancer Associate will be added to the program during the 05 year of the grant. This associate will have rotations on medical oncology, therapeutic radiology, pathology and head and neck surgery. It is hoped that when the clinical cancer associate has completed the program, he/she will assume an academic position in a dental school or hospital. (2) The Head and Neck Tumor Board will meet on a monthly basis so that all head and neck cancer patients are presented for general discussion. (3) A method of evaluation for the program comparing and contrasting it with other clinical cancer education programs, as well as comparing our objectives with those published by the

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Subcommittee on Dental Oncology will be implemented. (4) An attempt will be made to distribute the Colorado Oral Cancer Bulletin to states adjacent to Colorado. The Bulletin will serve as an educational vehicle for all health professions engaged in head and neck oncology. (5) Long term follow-up of tumor registry cases will be implemented to determine if a central tumor registry is of management significance to the patient and educational value to the students, residents, and fellows.

Grant 21241: Clinical Cancer Education Grant

From 7/1/78 to 06/30/84 FY 81: \$43,296
Dr. Sanford Leikin, Children's Hospital National Medical Center
Michigan Avenue, Washington, D.C. 20010

Objectives: A. Coordination and improvement of the Pediatric Oncology education program of the George Washington University School of Medicine and the Children's Hospital National Medical Center. B. Continuing Pediatric Cancer Education for Practicing Physicians. C. Preparation of audiovisual material concerning pediatric cancer which can be used in A and B above. D. Preparation of literature on pediatric oncology for families of patients with these illnesses.

Accomplishments: These will be described under each objectives. A multidisciplinary cancer education committee has been formed to supervise the implementation of cancer education objectives.

- A.1. Incorporation of a three-hour seminar on childhood leukemia into second-year core curriculum for medical students.
2. Lectures and informal seminars on pediatric oncology and psychosocial aspects of disease for third and fourth-year medical students and pediatric residents.
3. Restructuring of elective experience in pediatric oncology for medical students and residents.
4. Development of a lecture series for dental and surgical residents.
5. Support for training of three clinical associates in clinical oncology and basic research techniques.
6. Support for three clinical assistants who performed basic laboratory research in immunological aspects of pediatric oncology with clinical correlation.
8. Completion of three twelve-week pediatric oncology courses for nurses.
9. Completion of a one-day symposium for nurses on "The Child with Cancer - New Directions in Care".
10. Development of an interhospital seminar series on pediatric oncology.
11. Development of a list of objectives and objective and subjective evaluations for above educational endeavors.

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- B.1. Preparation of a bi-monthly newsletter entitled "Trends in Tumor Management - A Newsletter for the Pediatrician" distributed to 1200 pediatricians in the area.
- 2. Delivery of lectures on pediatric oncology to numerous community hospitals in the area.
- C.1. A videotape on "The Presentation of a Life-Threatening Diagnosis" has been completed and is used as a focus for discussion of these sensitive issues for medical students, residents, and nurses.
- D.1. A two-part booklet has been prepared for parents of children with Wilms' Tumor, neuroblastoma, rhabdomyosarcoma and Hodgkin's disease.
- 2. A parents' guide has been prepared describing the Department of Oncology and the roles of members of the interdisciplinary team.

Plans: The program for the next year will emphasize education in all aspects of supportive care and the ability to communicate in a supportive manner with the cancer patient and his family. This will be aided by the development of a program for residents in communication skills using simulated parents and videotaping. A program to educate teachers about the prognosis and capabilities of the child with cancer is also proposed. Plans also include development of slide cassette lectures on chemotherapy and supportive care and booklets on radiotherapy and brain tumors, bone tumors, and non-Hodgkin's Lymphoma.

Grant 21254: Adjustment and Adaptation in Children with Cancer

From 09/01/77 to 08/31/81

FY 81: \$206,000

Dr. John J. Spinetta, San Diego State University, Department of
Psychology, San Diego, California 92182

Objectives: The objectives of the project were: (1) to test for the presence of trends in the psychosocial reaction of the child to cancer and its treatment, and (2) to test methods for the reduction of any emotional, social, and/or academic dysfunctioning in the child with cancer which may result from the illness and treatment, so that the child can continue to participate as fully and successfully as possible in family, community, and regular school life. Studying the child's responses over time was aimed at resolving some of the inconsistencies in published cross-sectional research regarding the child's long-range coping abilities.

Accomplishments: The testing for the presence of trends has come from careful and methodic measurement of the child (attitudes and behaviors) over time, in response to his/her environment (personal, familial, and situational). A longitudinal series of measurements has been taken in a variety of contexts. During the three years of the project, 120 families from the two participating hospitals have been entered in some part into the study. Over 4,500 tests and measures have been administered to patients, siblings, and parents. Because of the longitudinal nature of the study, final data analysis was postponed until two-and-one-half years of data had been collected. The current analyses are taking into account the course of the disease process. This allows for an analysis of actual coping behavior over time, taking into account situation-specific fluctuations.

Comparisons were drawn of the two types of intervention across hospitals: (2) active-preventive, and (b) crisis-oriented. Initial cross-sectional analyses of data based on first administrations to family members did not point to significant differences between intervention modes across hospitals. Data analysis of longitudinal measures is helping to pinpoint within-hospitals factors affecting emotional response, such as disease stage, level of physical discomfort, age of child, and family support and communication patterns.

Results of initial data analyses have demonstrated the effectiveness of certain interventions, notably the school liaison program and the self-relaxation training. The testing of methods for the reduction of academic dysfunctioning has led to several conclusions to date. The child cancer patients present school-related problems not evident in their control peers. Serious learning problems arise most frequently among those patients who have received cranial radiation. Timely intervention with parents and teachers can effectively facilitate the child's return to school and can help resolve serious school-related problems.

Program Director: Sandra M. Levy, Ph.D.

From 04/01/77 - 03/31/83

FY 81: \$9,936

Dr. Alfred Hutchinson and Dr. Gary A. Jacobsen, Oregon Comprehensive Cancer Program, 3181 S. W. Sam Jackson Park Road, Portland, Oregon 97201

Objectives: This statewide voluntary cancer control network of metropolitan and community hospitals and health care organizations has as its primary objective the sharing of available professional and educational resources. The purpose of this sharing is to increase the availability of cancer control resources and information in Oregon communities so that all aspects of interdisciplinary cancer care are available to individuals as near as practical to their homes. Interdisciplinary cancer care focuses on the patient-family as a treatment unit with services delivered by a team composed of the appropriate physician and non-physician specialties.

Accomplishments: The Oregon Comprehensive Cancer Program (OCCP) accomplished the development of a statewide cancer control program where credibility has been achieved. (1) The number of member agencies has grown from 33 in 1980 to 50 in 1981 (30 hospitals and 20 major health care groups). These hospitals account for over 65% of beds in the State and 95% of all new cancer patients. (2) Ten additional hospitals are in the development process. (3) OCCP's medical director serves as a technical advisor to the HSAs and SHPDA regarding hospice. (4) The nursing continuing education program has had nearly 400 nurses complete the 40-hour Unit I course conducted in 12 geographic locations. A 45-hour Unit II course is being offered in 1981. (5) The Oregon Cancer Data Program is coordinating tumor registry data management services for 35 Oregon and 11 Washington hospitals. Fifteen-thousand new cases were added in 1980. (6) The distribution list of "The Cancer Newsletter," a quarterly clinical and patient management publication of OCCP, has grown to 6,500 in 1980. (7) A national survey of 44 oncology units resulted in the publication Oncology Units - The State of the Art. A two day National invitation working conference is scheduled and consensus statements are expected. (8) Statewide organizations for cancer physician specialties, oncology nurses, tumor registrars and hospice programs have been formed and are meeting regularly. The Oncology Nursing Society is establishing local groups throughout the state.

Plans: Six goals with 38 objectives approved by the OCCP Board for phase-in during 1980-83 include: (1) expanding and solidifying the statewide organization; (2) disseminating up-to-date cancer information as requested by OCCP members; (3) upgrading cancer nursing skills of Oregon nurses; (4) conducting special activities to meet identified cancer control needs; (5) running a financially independent data program, promoting the tumor registry as an integral component of community cancer control and; (6) securing non-NCI funding for OCCP continuation beyond 1983.

Program Director: Margaret E. Holmes, Ph.D.

Publications:

Jacobsen, G.A.: Helpful Hints for Hospice Caregivers, National Hospice Organization Annual Meeting Bulletin, November 15, 1980, p 2.

Jacobsen, G.A., Wright, C.C., DeMent, P., Berman, Fl, Deisher, R.: Oncology Units--State of the Art: Oregon Comprehensive Cancer Program, Portland, Oregon, 1980, 34 pp.

Form 07/01/77 to 06/31/83

FY 81: \$123,158

Dr. Kent Westbrook, University of Arkansas College of Medicine
Little Rock, Arkansas 72201

Objectives: This program is designed to improve the length of survival as well as the quality of life of patients with malignant diseases through education of medical students, residents, associates, practicing physicians and other health care professionals. Specific objectives include the support of the basic curriculum, the stimulation of active participation in tumor boards, the development of an experimental cancer teaching center, and support of post-graduate conferences including the Arkansas-Oklahoma Cancer Forum. The program draws upon the University Medical School Faculty, both full-time and part-time, to present the management of the cancer patient as a multi-disciplinary oncology problem.

Accomplishments: (1) Clinical Correlation Conferences have been instituted in the freshman year and have been a major component of the pathology course in the sophomore year of medical school. (2) Our basic Tumor Board is attended by approximately 30 to 40 individuals weekly. (3) The Arkansas-Oklahoma Cancer Forum is sponsored with the American Cancer Society annually in Fort Smith, Arkansas with an attendance of 400 professionals. (4) Sixteen clinical assistants are supported each summer in a program involving exposure to all oncology specialties and with emphasis on epidemiology and preventive oncology. (5) One clinical associate is supported each year, the first one was in head-and-neck surgery. (6) A Cancer Teaching Center has been developed with audiovisual aids in a modular fashion. All students are required to complete all modules during their junior rotation on Surgery. (7) Some administrative and financial assistance has been made available to hospitals throughout the state including the Area Health Education Centers to sponsor tumor conferences. (8) Professional assistance has been rendered to the American Cancer Society and to local individuals in the development of cancer programs for ministers. (9) A chapter on thyroid cancer for a major surgical oncology text have been completed in the last year.

Plans: Immediate future plans call for continuation of all programs currently active. A report summarizing our experience with the Cancer Teaching Center will be prepared for publication in the next year. A cancer conference for medical students from a five state area will be co-sponsored in Little Rock with the American Cancer Society. Extension of activities into hospitals and medical societies through the state utilizing tumor conferences and tumor boards will be expanded.

Program Director: Margaret H. Edwards, M.D.

Grant 21480: Changes in Mouse Colon During Chemical Carcinogenesis

From: 08/01/87 to 07/31/81

FY 81: -0- (Ann. \$34,332)

Dr. Thomas C. Richards, Ph.D., University of Oregon Health Sciences Center School of Medicine, 3181 S.W. Sam Jackson Park Road, Portland, Oregon 97201

Objectives: The overall objective of this project is to analyze changes in several indices of the cytokinetics of mucosal glands during dimethylhydrazine (DMH)-induced carcinogenesis to understand better the cellular basis for the sequential transformation of rapidly proliferating colonic epithelium. We propose to determine the reversibility of early changes in colonic mucosa induced by DMH; to measure changes in the rate of migration and turnover of cells from crypts in carcinogen-treated animals; and to determine whether low dose irradiation disrupts the organization of crypts sufficiently to alter the susceptibility of the mucosa to the carcinogen.

Accomplishments: The induction of adenocarcinomas in distal colon of mice by DMH is preceded by the development of hyperplastic mucosal glands. It has been determined that once induced changes in the mucosa progress to some threshold level (8 or more treatments with DMH), crypt glands are irreversibly enlarged and the development of tumors irrevocable. The atypias do not regress nor do the total number of cells/crypt decrease significantly. Even in those glands in which there were no visible lesions. Tumors eventually develop in these groups after a latent period whose length is inversely related to the number of treatments.

The mitotic activity of proliferative cells in crypts is a function of their position in the crypt column. Increased mitotic pressure induced by DMH leads to a faster rate of migration of cells toward the surface, gradually lengthening the crypts because immature cells reach the upper crypt and are retained. Crypts also increase in breadth during treatment because daughter cells that cannot migrate upward at a rate equal to production from mitosis are pushed laterally at the crypts base resulting in increased numbers of cell columns/crypt.

A compensatory surge of ^3H -thymidine labeled cells/crypt was observed in irradiated mice as cells in the lower crypt divide rapidly to replace the cells killed by irradiation. The response of the mucosal cells to the irradiation was amplified after DMH treatment because a larger population of cycling cells was at risk. The DMH-irradiation group has significantly less focal atypias and tumors than the DMH only group. This suggests that cells which had been altered with carcinogen were sloughed after irradiation. As a result, the progressive accumulation of specific changes in the crypt cells was delayed in the DMH-irradiation group.

Plans: Colostomies of the mid-left colon will be performed in order to determine if DMH-induced alterations are either promoted or inhibited in the proximal, functional segments and the distal, isolated segments. Cytokinetic changes in crypts that may underlie differences in response of the two colon segments to the carcinogen will be studied.

Publications:

Richards, T.C.: Changes in Crypt Cell Populations of Mouse Colon During Recovery from Treatment with 1,2-Dimethylhydrazine. J. Natl. Cancer Inst. 66:

Program Director: Vincent J. Cairolì, Ph.D.

Grant CA 21520: Heterogeneity of Human Colonic Carcinoma

From 02/01/78 to 01/31/84

FY 81: \$78,445

Dr. Michael G. Brattain, University of Alabama in Birmingham, University Station
Birmingham, AL 35294

Objectives: 1) The evaluation of the mechanism by which fibroblasts enhance the growth of human colonic carcinomas; and 2) the isolation and identification of subpopulations of malignant cells from individual human colonic carcinomas.

Accomplishments: We have developed methodology for the tissue culture of surgical specimens of human colonic carcinoma using feeder layers of fibroblasts to obtain long term cultures from 80-85% of the tumors attempted. This methodology will allow for the identification of heterogeneous types of malignant cells from the same carcinoma. The growth of cultured human colonic carcinoma and primary tumors were enhanced by feeder layers of confluent murine fibroblasts (C3H 10T1/2 cells). Feeder layers of fibroblasts stimulated colony formation from 2-9 fold for the 5 established cell lines tested. The effects of feeder layers of C3H 10T1/2 cells in the establishment of human colonic carcinoma were determined with 27 tumor specimens. Of the 27 specimens obtained, 21 were successfully established on feeder layers. All of these except one have been sub-cultured at least 5 times and have been maintained in tissue culture for 6-12 months. Three of the specimens did not grow at all, while 3 other specimens showed some initial growth in primary cultures but failed to survive attempted sub-culture. By contrast, when feeder layers were not employed only 3 specimens grew and survived passage in culture.

Cultures of tumors exhibited several types of morphology by phase contrast microscopy. These types are described as epitheloid, grape-like clusters, and small dark cells which grow in a rather disorganized manner. More than one type of growth pattern was most frequently observed.

Plans: The isolation and characterization of factors produced by C3H 10T1/2 cells which enhance growth of colonic carcinoma and the isolation and characterization of the subpopulations of malignant cells. These characterizations include tumorigenicity in nude mice, determination of growth parameters, colony forming ability in semi-solid medium, and analysis of cell surface radiolabeled proteins and glycoproteins.

Publications:

Brattain, M.G., Strobel-Stevens, J., Fine, D., Webb, M. and Sarraf, A.M.: Establishment of Mouse Colonic Carcinoma Cell Lines with Different Metastatic Properties. Cancer Res., 40:2142-2146, 1980.

Brattain, M.G., Fine, W.D., Khaled, F.M., Thompson, J. and Brattain, D.E.: Heterogeneity of Malignant Cells from a Human Colonic Carcinoma. Cancer Res., 41, 1981 (June issue).

Program Director: Vincent J. Cairolì, Ph.D.

Grant 21555: Clinical Cancer Education Program

From 07/01/77 to 06/30/84

FY 81: \$276,903

Dr. Saul Rosenberg, Stanford University School of Medicine
Stanford, California 94305

Objectives: The objectives of the Clinical Cancer Education Program are to (1) integrate and expand cancer teaching to medical students at their preclinical and clinical levels; (2) expand and strengthen postdoctoral clinical fellowship programs in the major clinical subspecialties; (3) expand multidisciplinary patient management programs; (4) improve oncology nursing programs in adult and pediatric areas; and (5) increase postgraduate cancer education activities for community physicians.

Accomplishments: These include (1) development of a new interdepartmental medical student course for preclinical students which is an introduction to cancer medicine; (2) development of strong subspecialty fellowship programs in radiation therapy, medical oncology, surgical pathology, and pediatric oncology with increased multidisciplinary emphasis and electives; (3) development of an integrated oncology inpatient service which hospitalizes patients from academic medical oncology, community medical oncology, and radiation therapy and the clinical research center; improved teaching on this Joint Oncology Service has resulted for subspecialty fellows, medical interns and residents, and medical students; (4) strengthening or initiation of nineteen multidisciplinary patient care clinics and boards, twelve in adult oncology and seven in pediatric oncology; (5) development of a school reentry program for children with cancer by sending a pediatric oncology nurse educator to schools which have or may enroll children under treatment for cancer; (6) expanded community outreach programs through the Northern California Oncology Group community clinical trial program; and (7) development of formal postgraduate courses and symposia for cancer-related topics.

Plans: This will include expansion of the cancer education programs by adding a pediatric oncology clinical associate during the coming year and a gynecologic oncology clinical associate in 1982. These additions will strengthen the multidisciplinary clinics, conferences, and premedical student course. An intensive course in Adult Oncology Nursing has been planned and will enroll its first students from the Stanford Hospital and community hospitals in the region this spring. Evaluation efforts will continue, especially for courses and student groups.

Program Director: Margaret H. Edwards, M.D.

From 09/30/77 to 07/31/83

FY 81: est. \$116,599

Dr. F.J. Chlapowski, Department of Biochemistry, University of Massachusetts Medical School, Worcester, Massachusetts

Objectives: The overall objective of the project is to develop an in vitro model of chemical carcinogenesis in homogeneous urothelium that closely approximates development of urinary bladder cancer in vivo. The value of such a model would be to allow precise physiological, biochemical and morphological studies that describe and compare the normal mechanisms of growth and differentiation to those of the carcinogenic process. It has not been possible to conduct such studies in vivo due to the microscopically thin nature of the tissue and its relative insignificance when compared to the bulk of other tissues composing the urinary bladder. An epithelial growth system which allows the growth, stratification, differentiation, and maintenance of homogeneous, adult Fischer-344 rat transitional epithelium in vitro has been developed. Using this system it is proposed: (1) to further define the requirements and factors governing growth, stratification, differentiation, and maintenance of normal tissue and; (2) to determine the biological mechanism of carcinogenesis in vitro. The normal tissue studies will include: continued development of a defined media; evaluation of porous growth surfaces; examination of the apparent differentiation-inducing effects of urine; determination of permeability characteristics; and resolution of the role of hormone-stimulated cyclic AMP metabolism in normal tissue. The carcinogenesis studies will include: determination of efficacious carcinogens; definition of morphological staging of in vitro carcinogenesis; assessment of the role of promoters; and analysis of a variety of events important in a two stage mechanism of carcinogenesis (e.g., dose effects, sequence, reversibility-irreversibility; cell division, etc.). Tumorigenicity of in vitro transformed cell lines will be determined by back-transplantation. These studies are being carried out to lay the foundation for determination of the molecular mechanism of chemical carcinogenesis of transitional epithelium.

Accomplishments: Since September 30, 1980, the following has been accomplished:

(1) The hormone (catecholamine) and prostaglandin (PGE₁) responsiveness of normal epithelial cultures and four FANFT transformed cell lines has been characterized with respect to cyclic AMP accumulation, adrenergic receptors, and cyclic AMP- and cyclic GMP-dependent phosphodiesterase. Each tumorous cell line was found to be defective in one or more aspects of cyclic AMP-dependent phosphodiesterase; (b) loss of cyclic GMP-dependent phosphodiesterase activity; (c) aberrant b-adrenergic receptors; (d) loss of functional PGE₁ receptors; and (e) loss of functional catecholamine receptors. However, no one specific defect was found to be common to all the tumorous cell lines and no correlation between these defects and tumor forming ability was observed. (2) A serum-free defined medium has been developed which allows growth of the normal urothelium for up to 3 weeks. (3) The morphological effects of the carcinogens ANFT, BCPN and DMBA have been observed following addition to normal cultures. Abberant morphology and growth patterns inevitably follow several weeks of exposure to nontoxic levels of these carcinogens.

The following study has been initiated and is in progress. Cultures of normal cells are exposed to either control media or media containing each of the four

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carcinogens for two to eight weeks. Those cultures exposed to control or carcinogen-containing media for two weeks are exposed to either control media or media containing one of 3 potential promoters (i.e. phorbol ester, urea, or saccharin) for the remaining six weeks. During the eight week experimental culture period one-half of the cultures are repeatedly subcultured to induce cell division. During the course of the experiment, cultures are fixed for light and electron microscopic analysis. Following the eight week period the cultured cells are back-transplanted into weanling Fischer-344 rats to assess tumor forming ability. Using this protocol, the effects of the carcinogens and promoters, as well as the effects of the cell division will be assessed. In this manner it is hoped that the mechanism of carcinogenesis in vitro will be worked out.

Plans: The experiment designed to describe the mechanism of in vitro carcinogenesis will require the remainder of the project period.

Publication:

Hahn, G.L., Haynes, L., and Chlapowski, F.J.: Variations of Adenosine 3', 5'-Cyclic Monophosphate Levels in Four Chemically Transformed Rat Transitional Epithelial Cell Lines. J. Natl. Cancer Inst. 65: 657-662. 1980.

Grant CA 21623: Studies of Utah Colorectal Cancer Families

From: 04/20/78 to 03/31/81 FY 81: -0- (Ann. \$137,498)
Dr. Eldon J. Gardner, Utah State University, College of Science, Logan, UT 84322

Objectives: The objectives of this research are: to determine specific, cellular diagnostic criteria for Gardner syndrome (GS), familial polyposis coli, and hereditary discrete polyps of the colorectum, and to clinically evaluate prevention and cure for cancer. Some 20 people in our study families have died at early ages from colon cancer. Using this human model we are investigating cell transformation to malignancy, reverse transformation, cell kinetics in the origin of adenomas, and cancer and fibroblastic activity in postoperative desmoids and spontaneous mesenteric fibromatosis.

Accomplishments: We have observed 84 individuals with polypoid conditions in 9 clinics at the University of Utah Medical Center and in 2 rural Utah communities. These individuals have undergone extensive physical examinations with sigmoidoscopies or colonoscopies performed on 75 and esophagogastroduodenoscopy on 12. Results of these examinations have identified 41 individuals with colon polyps. Numerous extra colorectal lesions have been observed in GS patients, and 93 x-ray films of the maxilla and mandible are being evaluated for odontomas, osteomas, and supernumerary teeth. Potential life-threatening desmoid tumors have been found in 12 of 15 GS patients. In tissue culture, 59 skin and 3 colon polyp biopsies have been established. Chromosomes from 74 blood lymphocyte cultures have been evaluated for near diploidy and structural aberration using G-banding. We have continued to observe excessive new diploidy and a chromosome No. 2 polymorphism. Using sister chromatid exchange analysis and the measurement of difference in response to mitomycin-C challenge, a significant difference between controls, patients with solitary or few polyps, and patients with multiple polyps has been observed. Thirty-one sets of colon biopsies have been labeled with thymidine for cell kinetic studies; 78 additional samples are now in process.

Plans: We plan to monitor and record data on current, new, and control study families by meeting people in their homes and conducting clinics in the field and at the University of Utah Medical Center; and we expect to have 100 additional patients processed through our protocols at clinics at the University of Utah and in 3 or 4 rural Utah communities by September 30, 1981. Specimens will be obtained as warranted for the laboratory experiments enumerated above.

Publications:

Skolnick, M., Bishop, D.T., Carmelli, D., Gardner, E.J., Hadley, R., Hasstedt, S., Hill, J.R., Hunt, S., Lyon, J.L., Smart, C.R., and Williams, R.R.: A Population-Based Assessment of Familial Cancer Risk in Utah Mormon Genealogies. In Genes, Chromosomes, and Neoplasia, D.E. Arrighi, R.N. Rao, and E. Stubbelfield, Eds. New York, Raven Press, 1981: pp. 477-500.

Bishop, D.T. and Gardner, E.F.: Analysis of the Genetic Predisposition to Cancer in Individual Pedigrees. In Banbury Report 4: Cancer Incidence in Defined Populations, J. Darns, J.L. Lyon, and M. Skolnick, Eds. Cold Spring Harbor Laboratory, 1980; pp. 389-408.

Program Director: Vincent J. Cairolì, Ph.D.

From 08/01/77 to 07/31/81

FY 81: 0 (Ann. \$86,492)

Dr. Leon Gordis, Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, 615 N. Wolfe Street, Baltimore, Maryland 21205

Objectives: Pancreatic cancer is now the fourth leading cause of cancer deaths in the United States killing about 18,000 people in the country each year. Age-adjusted mortality rates have increased dramatically in the last 50 years. The importance of this disease is further underlined by its extremely bleak prognosis. Median survival time is two-three months; one year relative survival rate is about eight percent and the five year survival rate is only about two percent. The major hope for improvement in pancreatic cancer is through earlier diagnosis and development of effective measures for prevention. Prevention will require identification of specific etiology factors and of factors associated with high risk for this disease. If exposure to these factors can be reduced or eliminated, prevention may be possible.

The objective of this study is to compare epidemiologic characteristics of patients with pancreatic cancer and hospital and neighborhood controls in order to provide clues to the possible etiologic factors for this disease. The emphasis is on specific environmental and occupational characteristics, including occupational exposure to chemical agents, dietary factors, smoking, alcohol consumption and other characteristics of lifestyles.

Accomplishments: Sixteen hospitals in the Baltimore metropolitan area are participating in this case-control study of pancreatic cancer. These include all major hospitals in the area. As of April 21, 1981, 250 cases of pancreatic cancer have been interviewed. Since October 1, 1980, 60 new patients have been identified and interviewed. Since the project is due to end at the end of July, ascertainment of new cases has stopped. We are still interviewing both neighborhood and hospital controls. At the present time we have interviewed 180 neighborhood controls and 160 hospital controls. We have preliminary analyses of results on 107 of the case-neighborhood control pairs.

Of the cases interviewed thus far, 22 percent are black, 78 percent are white, 49 percent are females, 51 percent males and 70 percent are over 60 years of age. Although the overall age distribution does not vary greatly between males and females, it is of interest that a markedly greater number of the cases over 80 years of age are females. Only about half of all cases are histologically confirmed, and of these the overwhelming majority are adenocarcinoma. There is no indication thus far that the location of the tumor varies by sex. In the interim analysis of 107 case-neighborhood control pairs and a limited number of variables of interest, results have suggested the importance of dietary carcinogenesis, with elevated risks suggested for such food items as salami, bologna, bacon, sausage, eggs, and smoked fish or beef. A protective or reduced risk was suggested for frequent consumption of high fiber foods such as whole grain breads and raw fruits or vegetables. Smoking was weakly associated with an increased risk. A protective effect was suggested for tonsillectomy, which has also been reported for other cancers, but an increased risk was found for living on a farm and having farm animals and for low income.

Program Director: William E. Straile, Ph.D.

Plans: For the remainder of the grant period we plan to complete interviews with neighborhood and hospital controls and complete coding and analysis of the data. We will be looking further and in greater depth at the variables thus far suggested as risk factors for pancreatic cancer and adjusting the results for the possible confounding effects of other variables.

Grant CA 21656: Synthesis of Potential Bile Acid Metabolites

From 09/01/76 to 12/31/81

FY 81: \$74,145

Dr. Frederic C. Chang, University of South Alabama, Mobile, Alabama 36688

Objectives: The major objectives of this project are 1) to synthesize and characterize new and known, but generally unavailable, bile acid metabolites for use as reference standards by investigators involved in colon carcinogenesis research, and 2) to improve the methodology of bile acid synthesis, in particular to devise practical procedures for obtaining larger quantities of the more difficult compounds. The derivatives are being made available to investigators interested in clarifying the possible role of bile acids in large bowel carcinogenesis.

Accomplishments: A variety of dihydroxy, trihydroxy and related hydroxy and keto acids as well as the following cholanic acids have been synthesized: 3β , 7α -dihydroxy; 3β , 7α -dihydroxy; 7β , 12β -dihydroxy; 7β , 12β -dihydroxy and 7β , 12α -dihydroxy. Efforts continue in the synthesis of the remaining trihydroxycholanic acids of the 3,7,12-series. The syntheses include both the $5-\alpha$ and the $5-\beta$ cholanic acids. Each product has been purified and characterized spectrometrically.

Improved methodology for stereospecifically reducing C-12 ketones to 12β -hydroxy compounds is being developed. Methodological improvements are being made in converting production from small to large scale quantities and in using high-pressure liquid chromatography to identify bile acids.

Plans: It is planned to complete syntheses and to characterize the β -bromophenacyl esters of the novel acids for analytical purposes and to explore methods of preparing Δ^2 and Δ^6 -acids.

Publications: Iida, T. and Chang, F.C.: Potential Bile Acid Metabolites. 3. A New Route to Chenodeoxycholic Acid. J. Org. Chem., in press, 1981.

Program Director: Vincent J. Cairolì, Ph.D.

From: 06/01/77 to 05/31/82

FY 81: \$234,718

Dr. Arnold D. Welch, St. Jude Children's Research Hospital, 332 N. Lauderdale, Memphis, TN 38101

Objectives: Our objectives include a molecular explanation of the chemotherapeutic inactivity of 5-fluorouracil in 80% of human colorectal carcinomas in man; the significance of the low levels of uridine (urd)-cytidine (cyd) kinase in 86% of surgical specimens of these neoplasms; the relative importance of the salvage of urd and cyd vs. the biosynthesis de novo of urd monophosphate (UMP); development of new techniques for inhibiting the salvage of urd and cyd and of the de novo-pathway to UMP in vivo; characterization of an enzyme involved in the phosphorylation of urd and cyd and their cytotoxic analogs; elucidation of the mechanism of transport into cells of urd and cyd and its inhibition; further development of a potent murine anti-thymocyte serum (ATS) that enables human colorectal carcinomas to grow and to metastasize in mice; and chemotherapeutic studies of combinations of drugs (and enzyme inhibitors) in mice bearing xenografts of human colorectal carcinomas.

Accomplishments: A direct correlation has been found between the degrees of response of human colorectal xenografts to 5-fluoro-2'-deoxyuridine 5'-monophosphate (FdUMP) and the levels in the tumors of 5,10-methylenetetrahydrofolate, essential for the formation of a ternary complex of FdUMP, the folate-derivative, and thymidylate synthetase. The discovery of an alternative enzymic pathway for the salvage of nucleosides (other than that involving urd-cyd kinase) has placed new emphasis on salvage, in addition to that on the de novo-biosynthesis of UMP, upon which most colorectal carcinomas appear to be dependent for survival. For these reasons, extensive studies are in progress of maintained tissue levels of an analog of urd that is a substrate for both urd-cyd kinase and the "new" enzyme, while the metabolically formed monophosphate not only inhibits the last step in the de novo-pathway to UMP, but does not enter either RNA or DNA. In addition, efforts to isolate and characterize the "new" enzyme have now clearly indicated that it is not a phosphotransferase, neither is it deoxycytidine kinase nor adenosine kinase. Studies of the rapid phase of the facilitated diffusion of nucleosides into neoplastic cells (particularly of a mutant line lacking all nucleoside-phosphorylating mechanisms) has indicated the importance of charge; thus, the anionic species of some ribonucleosides appears not to utilize the "transporter" in the cell membrane, a phenomenon that could affect the projected chemotherapeutic use of inhibitors of the nucleoside-"transporter".

Plans: Logical extensions of each aspect described above will be made during the coming year, with special emphasis on the chemotherapy of human adenocarcinomas, grown either as subcutaneous xenografts or as metastatic tumors in immunodepressed mice. Using human neoplasms, as well as cells in culture, additional studies of enzyme patterns will involve not only the pathways of nucleoside-phosphorylation, and their inhibition, but also additional determinations of enzyme-activities (as well as their inhibition) in the de novo-pathway to UMP.

Publication: Houghton, J.A. and Houghton, P.J.: On the Mechanism of Cytotoxicity of Fluorinated Pyrimidines in Four Human Colon Adenocarcinoma Xenografts Maintained in Immune Deprived Mice. Cancer, 45:1159-1167, 1980.

Program Director: Vincent J. Cairoli, Ph.D.

From 08/01/78 to 07/31/81

FY 81: \$0 (Ann. \$77,516)

Dr. Alice J. Claflin, Department of Surgery, University of Miami School of Medicine. P.O. Box 016960, Miami, Florida 33101

Objectives: The Dunning R3327 transplantable prostatic adenocarcinoma and the sublines of this tumor represent a spectrum of growth rate and differentiation. The host immunological response to the tumor and the determination of immunological parameters during disease progression has emphasized the adequacy of this animal model for the human disease. Membrane glycoproteins purification and characterization has demonstrated differences associated with degree of differentiation. The characterization of these membrane components, their role in immunogenicity of the tumors and their association with a specific cell population within the tumor may provide insight into the mechanism of the disease.

Accomplishments: Our continued efforts in the studies of this animal model have emphasized its applicability as a model for the human disease. We have observed that direct cytotoxicity assay is correlated with tumor size. This observation has led to the measure of this *in vitro* immune reaction during progression of the disease. We have confirmed our initial observation that this immune function is lost as tumor size increases.

We have determined that the tumors consist of two cell populations, one diploid and one aneuploid. The diploid cells grow well in culture and when injected into animals, is tumorigenic. The tumors that result contain both diploid and aneuploid cells. Efforts are underway to determine culture conditions that will maintain the aneuploid cells in culture. The dispersed tumor cells have been cloned in soft agar and these cell populations are presently being investigated.

Centrifugal elutriation of dispersed tumor cells may isolate diploid and aneuploid cells. The subsequent isolation and purification of membrane glycoproteins of these cells will be carried out. 2-D gel electrophoresis may give further insight into differences at the cellular level of this tumor model. Antibody has been produced to tumor cells and immuno affinity chromatographs used to further purify the membrane antigens. It will also be produced to pure populations of separated diploid and aneuploid cells.

Plans: Our project will continue through July. Centrifugal elutriation will be well underway during this period and the measurements of direct cytotoxicity during progression of disease will be completed. 2-D gel electrophoresis of tumor cells and normal rat prostate will be completed during this time.

Publications:

Collins, J.M., Bagwell, C.B., Block, N.L., Claflin, A.J., Pollack, A., Irvin, G.L. and Stover, B.: Flow Cytometric Monitoring of R3327 Rat Prostate Carcinoma. Invest. Urol. (in press) 1981.

Program Director: Andrew Chiarodo, Ph.D.

Claflin, A.J., Pollack, A., Block, N.L., Irvin, G.L. and Malinin, T.I.: Production of Tumors with Diploid and Aneuploid Cells by Predominantly Diploid Culture Cells. Fed. Proc. 1981.

Pollack, A., Claflin, A.J., Irvin, G.L. and Block, N.L.: Flow Cytometric Analysis of Well and Poorly Differentiated Rat Prostate Carcinoma. Fed. Proc. 1981.

Kozlovskis, P.L., Claflin, A.J., Gratzner, H.G., Rubin, R.W., Fletcher, M.A. and Malinin, T.I.: A Cell Line Derived from a Rat Prostate Adenocarcinoma. Fed. Proc. 40:784, 1981.

From 09/01/77 - 03/31/83

FY 81: \$162,821

Dr. Roland T. Skeel, Medical College of Ohio, Toledo, Ohio 43699

Objectives: The goal of the Northwest Ohio Cancer Network Outreach Program is to develop an area-wide community outreach program in cancer control organized through the Northwest Ohio Cancer Network in order to bring the most effective prevention, detection, diagnosis, pretreatment evaluation, treatment and rehabilitation management possible to the people of northwest Ohio. The Medical College of Ohio (MCO) is the sole medical school serving the twenty-county area of northwest Ohio. As such, it serves a major role in health care education, program planning and development.

Accomplishments: (October 1, 1980 to September 30, 1981):

(1) A continuing cancer control needs assessment has been carried out through the development of regional councils formed in the twenty-county northwest Ohio area. The councils are comprised of physicians, hospital administrators, nurses, business and health agency representatives, volunteers and special interest group members. (2) In addition to professional education for physicians and nurses, network programming has expanded to include allied health professionals. Traveling tumor seminars continue to be given in 7 different community hospitals throughout northwest Ohio. Each hospital has four to ten seminars a year with participation of from 8 to 25 physicians and nurses at each seminar. An oncology nursing educational needs assessment survey was developed by the Network and distributed to nursing personnel of 23 hospitals of more than 100 beds in northwest Ohio. Of the 1,754 distributed, 1,133 completed surveys were re- (a return rate of 65%). A Network sponsored seminar on pain management was attended by 80 physicians and nurses from northwest Ohio. Allied health programs included a) a workshop entitled "Comprehensive Rehabilitation of the Cancer Patient" which was attended by occupational and physical therapists; b) a conference entitled "Smoking in the Workplace" for business, industry and hospital representatives; and c) a workshop on establishing support groups for patients with life threatening illness designed for social workers, pastoral care personnel, etc. (3) Network staff support has been given for the development of a proposal to facilitate the implementation of the school health curriculum project (Grade 5 - respiratory system) in northwest Ohio Schools. (4) The Northwest Ohio Cancer Network News is published 4 times yearly and reaches over 2,500 health care providers and consumers in the twenty-county area. (5) Planning for clinical care programs has involved staff support for community initiated projects in Hospice, in multi-hospital clinical oncology programs (Toledo Community Hospital Oncology Program) and an MCO multi-institutional clinical cooperative group program.

Plans: Plans for the Northwest Ohio Cancer Network Outreach Program for the remainder of the project period include furthering the development of regional council activities in conducting ongoing inventories and analyses of existing cancer management resources, patient numbers and patient flow patterns within northwest Ohio and developing an area cancer plan based on regional council findings, recommendations and expressed needs.

Program Director: Margaret E. Holmes, Ph.D.

Publications:

Becker, T.M.: Cancer Chemotherapy, A Manual for Nurses. Boston, Little Brown and Co., 1981.

From 07/01/77 to 08/31/82

FY '81: \$96,273

Dr. Richard B. Warnecke, Illinois Cancer Council, 36 South Wabash Avenue
Chicago, Illinois 60603

Objectives: The general goal of this project is to determine and evaluate the most effective means of communicating information about prevention and early detection of cancer of specific sites (breast, cervix-uterus, colon-rectum, prostate, skin, and lung) to rural and urban population groups in Illinois who fall in the lowest third of the population in income and who were born before 1942, and to identify other factors that might inhibit or facilitate behavior once proper motivation and information are present. The project included a baseline survey to determine existing knowledge, beliefs, behavior, and access to care; mailing of an experimental communication tailored to the needs and characteristics of the group under study; and evaluation of the short-term and long-term effectiveness of such communication. The final phase of the study will be a survey of the health care providers for the panel members, to determine their attitudes toward prevention and early detection of cancer, and what practices they currently follow.

Accomplishments: In this study a panel survey design was used in which four phases of interviews were conducted. In the initial phase, or baseline, a telephone sample of the general population of Illinois was screened to locate eligible respondents who were then interviewed about their current knowledge, beliefs and behavior relevant to the prevention and early detection of cancer. This phase was completed in April 1978. In the second phase, respondents to the baseline were interviewed in person to obtain an signed consent form authorizing verification of preventive care with their health care providers. This phase was completed in January 1979. Verification procedures with the health care providers were conducted by mail, with repeated telephone follow-up when necessary to secure cooperation, and were completed in May 1979. In May 1979 the mailing of the experimental communication was also completed; this communication was designed in the format of a newspaper similar to such tabloid as the National Enquirer. On the front page an easy to read "Table of Contents" described the major features in the four-page newspaper. Each feature was site-specific and directed toward a particular belief assumed to be important in producing preventive behavior according to the theoretical model adopted for this study. Thus, the format was designed to help the respondent select the specific information relevant to his/her information needs. Half of the sample received this communication; the other half, to be used as a control group, received letters that reminded them to keep the study staff advised of their whereabouts. In the third phase of data collection, conducted in October-November 1979, a telephone interview was again held with each respondent in the panel to ascertain changes in knowledge, beliefs, and behavior. A consent form to verify the preventive behavior reported as having occurred since the previous interview was obtained by mail, and verification with the health care providers was again conducted. This phase was completed in March 1980.

To evaluate the long-term effects of the communication, a second follow-up survey of the panel members was conducted in January and February 1981, approxi-

Program Director: Carlos E. Caban, Ph.D.

mately eighteen months after the mailing of the communication. Consent forms for the verification of reported preventive behavior are now in the process of being collected, and verification procedures with the health care providers are expected to be completed in May 1981. After completion of the panel study, a mail questionnaire will be sent to all physicians contacted in any of the three verification phases, to ascertain their attitudes toward prevention and early detection of cancer, and what tests and examinations they routinely provide to asymptomatic patients. The physicians' data will be analyzed both by itself as a survey of the position of physicians in Illinois on the issue of cancer prevention, and in conjunction with the data from the panel study; each patient's data will be matched with the corresponding physician's data, to obtain a balanced picture of the interaction between the patient and the provider, and its implication for health behavior. This phase is expected to be completed by August 1981, and it will terminate the data-collection part of the project.

Plans: Although preliminary analysis of the data was done as each wave was completed, a comprehensive analysis and writing up of the findings was postponed until all data was collected, including that of the extension of the project with the second follow-up survey and the physician's survey. The final year of the project, from 09/01/81 to 08/31/82, will be devoted to the computer linkage of all the phases, comprehensive data analysis of the entire study, and reporting of findings.

From 07/01/77 to 06/30/82 FY 81: \$130,407
Tapan A. Hazra, M.D., Medical College of Virginia
Box 533 MCV Station, Richmond, VA 23298

Objectives: The Clinical Cancer Education Grant is designed to improve the quality of cancer education at the undergraduate and graduate levels through: (1) analysis of the organ-system undergraduate curriculum in terms of its coverage of oncology objectives; (2) development of a comprehensive oncology test-item bank; (3) development of innovative teaching mechanisms in cancer; (4) implementation of coordinated multidisciplinary clinical electives for both the preclinical and clinical years; (5) inclusion in graduate training of specific exposure to both multidisciplinary diagnostic/treatment planning and the oncologic aspect of the disciplines of surgical pathology and radiation therapy; (6) development of Clinical Cancer associateships with specialized competence in specific areas of oncology along with exposure to complementary disciplines important to the multidisciplinary approach to the cancer patient.

Accomplishments: (1) Development and implementation of a system for analyzing the preclinical curriculum in terms of oncology coverage by categorizing and coding course syllabi and student lecture notes. (2) Development and implementation of a system for analyzing the clinical curriculum in terms of oncology coverage by having students code "cancer educational events" on a Daily Log Form. (3) Development of the Interinstitutional Oncology Item Bank, containing 1,500 test items keyed to the "Handbook of Objectives in Oncology." (4) Promoting the development of student self-assessment skills through utilization of a series of workbooks (developed to correspond to the topics in the "Handbook of Objectives in Oncology"), each containing objectives, a literature review, and a quiz. (5) Clinical Associateships: two in Radiation Therapy, two in Medical Oncology, one in Surgical Oncology, and one in Hematology. The associates rotate through oncology disciplines other than their parent oncology specialty; attend from four to eight oncologic seminars and planning conferences each week; are involved as a group in more than 15 research efforts involving laboratory, clinical, and literature review aspects of cancer; and lead daily rounds with emphasis on case discussion. (6) Clinical Assistantships for six M-I and M-II students during the summer of 1980, having a multidisciplinary clinical focus. Included in the program were rotations through radiation therapy, diagnostic radiology, tumor clinics, cancer rehabilitation, along with a series of 14 seminars covering different aspects of oncology. (7) Colorectal Cancer Conference in March, 1980, attended by students and residents. (8) Symposium on Coagulation Disorders in Hematological Malignancy in October, 1980, attended by students and residents. (9) Radiotherapy Lecture Series for M-IV students. (10) Initiation of a multidisciplinary Lymphoma Conference. (11) Six visiting guest professors at various times during the period from February, 1980 to February, 1981.

Plans: The oncology curriculum analysis will continue, culminating in a plan for consolidation, reorganization, addition, and elimination of content, as appropriate. A comprehensive cancer knowledge test will be constructed

Program Director: Margaret H. Edwards, M.D.

from the Item Bank, validated on students, and used as an "output" measure to supplement the curriculum assessment. Innovative teaching mechanisms in cancer will then be developed, based on revealed deficiencies. The Clinical Associate and Assistant programs will continue, along with the various oncology lecture series, seminars, and rotations for undergraduates and graduates.

From 09/30/78 to 08/31/81

FY 81: \$74,514

Dr. James L. Talbert, Florida Association of Pediatric Tumor Programs, Inc.,
J. Hillis Miller Health Center, Box J-286, University of Florida,
Gainesville, Florida 32610

Objectives: (1) Rationale: Use of the cancer management resources of a coordinated statewide organization of pediatric oncology centers will improve the detection, treatment and monitoring of childhood cancer. (2) Significance: A statewide pediatric cancer treatment organization that encompasses large urban and rural areas with diverse often transient populations; and coordinates voluntary, state, federal, and private cancer control agencies to accomplish its goals and that can serve as an exemplary model for establishment of pediatric cancer programs or comparable adult oncology programs in other states or regions.

Accomplishments: (March 1, 1980 to February 28, 1980)

1. Each participating childhood cancer treatment center has received \$9,000 in grant support from the American Cancer Society, Florida Division.
2. A statewide pediatric tumor registry has been established and will be coordinated with the Pediatric Oncology Group Statistical Center in Gainesville and with the Comprehensive Cancer Center in Miami.
3. The FAPTP Statewide Patient Information Reporting System (SPIRS) has been implemented and 450 new patients accessed into SPIRS. A follow-up patient registration system has been initiated to assess the status of 1980 patients. Finally, SPIRS has implemented an epidemiology data collection system to identify unusual patterns of disease occurrence and possible etiologic factors.
4. State legislature designation of FAPTP as the advisory body for Children's Medical Services of Florida's Department of Health and Rehabilitative Services pediatric hematology/oncology services.
5. Creation of a Pathology Task Force to perform quality control for SPIRS, standardize pediatric oncology diagnoses, and review SPIRS results.
6. Successful Annual Childhood Cancer Treatment Seminar emphasizing increased participation in national study groups.
7. FAPTP was accepted as a member of the Florida Cancer Council.
8. A contract between the Children's Medical Services of the Florida Department of health and Rehabilitative Services for evaluation of pediatric hematology/oncology services.
9. Completion of a comprehensive psychosocial needs assessment of Comprehensive Childhood Cancer Treatment Centers to describe current services and identify psychosocial needs.

Program Director: Donald N. Buell, M.D.

Plans:

1. To develop a coordinated pediatric cancer public awareness program.
2. To initiate specific epidemiological studies to identify unusual patterns of disease occurrence and possible causative factors.
3. To improve quality of care provided by FAPTP Comprehensive Childhood Cancer Treatment Centers.
4. To identify mechanisms through which centers and communities can relate more effectively to insure availability of optimum care.
5. Establish and expand long-term monitoring and evaluation of childhood cancer patients.
6. Expand rehabilitation services.
7. Monitor and evaluate current management techniques for effectiveness and formulate new techniques.
8. Increase cost savings by:
 - a. Prevention and early detection of disease.
 - b. Early recognition and treatment of disease complications
 - c. Decentralization of treatment.
 - d. Coordination and sharing of related health services activities.

Grant 22063: Experimentally Induced Pancreatic Adenocarcinoma

From 07/01/77 to 06/30/81

FY 81: 0 (Ann. \$43,420)

Dr. Dale E. Bockman, Department of Anatomy, Medical College of Georgia,
Augusta, Georgia 30912

Objectives: The results of our previous work indicated that, contrary to the common opinion, pancreatic tumors arising as a result of chemical carcinogenesis in experimental animals were not derived exclusively from ductal cells, but could also arise from acinar cells. We wanted to test this hypothesis in experimental animals and to determine the extent to which a similar view was applicable to human pancreatic adenocarcinoma. Our overall goals are to determine the cells of origin of pancreatic carcinoma and to establish the conditions which develop or change and lead to the earliest lesions. This approach includes a consideration of the possibility that carcinogenic agents are more likely to act at a time when the pancreas is being nonspecifically altered by that agent or another agent or condition.

Accomplishments: Our view that acinar cells may be transformed during or after phenotypic modulation ("dedifferentiation"), subsequently being recognized as carcinoma of ductular origin, is based on a previous suggestion that the zymogen granule-containing cells of pancreas are not arranged like branches of grapes (acini) but are essentially tubular. This view was confirmed by injecting microscopy and cone rubber substance into the pancreas and studying it by light microscopy and scanning electron microscopy. We also showed that ligation of the pancreatic duct in animals leads, within four days, to "ductular" changes, quite similar to those observed with carcinogenesis, which are actually acinar cell changes. Animal models were compared with areas of "ductular proliferation" in human pancreas. Remarkable similarity was demonstrated. The enzyme markers alkaline phosphatase and gamma glutamyl transpeptidase were found not to be useful in differentiating ductal cells from acinar cells during carcinogenesis.

Plans: We plan to study the normal architecture of the normal human pancreas, and to compare normal pancreas with pancreatic adenocarcinoma and chronic pancreatitis from humans by means of electron microscopy in order to verify the applicability of observations in animals to human disease. We plan to develop monoclonal antibodies to acinar and ductal cell components to serve as probes for determining the cell of origin of pancreatic adenocarcinoma. Utilization of receptors for muscarinic neurotransmitters, cholecystokinin, and cholera toxin will also be used as markers. A careful assessment of pancreatic organogenesis in humans is planned, as is a comparison of the biochemical and quantitative morphometric changes induced by carcinogenesis and by ductal ligation.

Publications:

Bockman, D.E.: Architecture of normal pancreas as revealed by retrograde injection. Cell Tiss Res 205:445-451, 1980.

Bockman, D.E.: Cells of origin of pancreatic cancer: Experimental animal tumors related to human pancreas. Cancer 47:78-84, 1981.

Program Director: William E. Straile, Ph.D.

Grant CA 22071: Cancer Control Developmental and Support Grant

From 09/30/77 - 01/31/81

FY 81: 0 (Ann. \$38,000)

Leslie W. Whitney, M.D., - 1202 Jefferson Street, Wilmington, Delaware 19801

Objectives: To provide administrative support for the continuation of a state-wide "state-of-the-art" cancer program.

Accomplishments: (1) Recruitment of staff to provide for implementation of goals and objectives including a full-time Director, Deputy Director, Business Manager, Executive Secretary and Clerical Staff; (2) Continued the development of "state-of-the-art" programs in cancer control to maintain comprehensive cancer care for the residents of the State; (3) Completed an assessment of cancer patients' social needs, and nurse education needs and published results; (4) Developed and published a patient resource guide; (5) Prepared multiple educational brochures for professional and patient use; (6) Continued monthly Cancer Communique; (7) Continued statewide morbidity study; (8) Compiled and began preparing for publication of the second edition of a three-year follow-up study of "Incidence and Survival Rates of Most Common Cancers in Delaware 1977-1979"; (9) Introduced legislative initiatives to fund statewide cancer programs and succeeded in establishing a State Tumor Registry; (10) Participated in State Health Planning; and (11) Succeeded in securing outside funding commitment for revision and publication of "Opening New Doors".

Plans: Program terminated on 01/31/81.

Publications:

Hayward, C.L., Pohlen, J.M.: Data Collection and Follow-up of 1,000 Delaware Patients with Breast Cancer. Delaware Medical Journal, 52: 311, 1980.

Whitney, L.: The Reorganization of the Delaware Cancer Network. Delaware Medical Journal, 52: 371, 1980.

Whitney, L.: Cancer Becomes a Reportable Disease in Delaware. Delaware Medical Journal, 52, 419, 1980.

Whitney, L.: Guidelines for Mammography. Delaware Medical Journal, 52: 471, 1980.

Whitney, L.: Adjuvant Chemotherapy of Breast Cancer. Delaware Medical Journal, 52: 515, 1980.

Marvil, C.D.: Terminal Care Seminar Report. Delaware Medical Journal, 52: 575, 1980.

Whitney, L.: Public Understanding of Breast Cancer Improves Outlook. Delaware Medical Journal, 25: 631, 1980.

Whitney, L.: Key Factors Essential in Hospital Medical Records for the Study of Breast Cancer. Delaware Medical Journal, 53: 83, 1981.

Program Director: Margaret E. Holmes, Ph.D.

Thawley, C., Stadnik, L.: Nutrition Information for Ostomates, Wilmington, DE. The Wilmington Medical Center Cancer Program, 1989.

Sachlteben, C., Wingate, B.: If the Trolley's in Sight..., Wilmington, DE The Wilmington Medical Center Cancer Program, 1980 Second Edition.

Stadnik, L.: Nutrition Information for Cancer Patients, It's Up to You: Wilmington, DE The Wilmington Medical Center Cancer Program, 1980 Second Edition.

From 08/01/79 to 11/30/81 FY 81: 0 (Ann. \$291,000)
Dr. Condit Moore, University of Louisville Regional Cancer Center
129 East Broadway, Louisville, Kentucky 40292

Objectives: The five main objectives of this grant are: 1) to systematically identify cancer control needs; 2) to expand relations with other cancer control activities in the region; 3) to develop evaluation measures for various projects; 4) to implement specific programs; 5) to identify an internal administrative structure that will support the various facets of these programs.

Accomplishments: During the year several needs were clarified for cancer control in this region; the main need for an increased multidisciplinary consultation system for each patient on first diagnosis. This need was made evident by a study of 950 head and neck squamous cancer patients, excluding skin, over a period of 20 years. The conclusion was that patients who had an initial single disciplinary treatment decision achieved a 25% rate of success, whereas those with two or more disciplines making the initial treatment decisions achieved nearly a 50% rate of success. Progress toward expansion of community relations and implementation of a project to fulfill this need has been made. An outpatient cancer center for multidisciplinary consultation to serve the regional practicing physicians has been built. Twelve million dollars in private community funds was contributed for the center and the building is ready for occupancy and function in August 1981. A regional Physicians Advisory Council and an Interhospital Cancer Committee have been formed. In addition, a joint Board of Governors of this Cancer Center combines University and community leaders, acts as the overall administrative responsible group. Approval by the Kentucky Medical Association and the Jefferson County Medical Society has been received. The Center will be staffed by full time faculty of the University of Louisville from the six oncology subspecialties. All funds generated go to the Center.

An evaluation plan has been developed to compare prospectively, by site and stage, outcomes from Center-served patients with outcomes from patients served by traditional patterns of referral in one community hospital. A second recent accomplishment is the establishment of a statewide cancer control plan with the University of Kentucky where new administrative leaders have established good communications and a genuine cooperative climate of helping each other help the whole state. A jointly supported consultant (John R. Durant, M.D.) will have visited Kentucky by May 19-20, 1981 to review, suggest, and help finalize these plans. A third recent accomplishment is the establishment of a clearinghouse at the Cancer Center for low cost (\$5.00 per night), short term housing for cancer patients and families coming to Louisville from rural areas for diagnosis and treatment. Also, a successful nutrition and cancer seminar has been held.

Plans: A permanent Cancer Control Director will be appointed as soon as funding for more than a year is available. Of course, the function of the multidisciplinary cancer center outpatient building and unit will begin in August, 1981 and proceed to collect data for the evaluation project.

Program Director: Margaret E. Holmes, Ph.D.

Publications:

Bland, K.I.; Buchanan, J.B.; Mills, D.L.; Kuhns, J.G.; Moore, C.; Spratt, J.S.; Polk, H.C., Jr.; Analysis of Breast Cancer Screening in Women younger than 50 years. JAMA, 245:10 1037-1042, March 13, 1981

From 07/01/77 - 07/31/83

FY 81: \$249,871 est.

Dr. Leonard E. Heller, Ephraim McDowell Cancer Network, 715 S. Limestone,
Lexington, Kentucky 40503

Objectives: The goal of the McDowell Cancer Network Community Outreach Program is the coordination, mobilization and implementation of cancer control programs in the state of Kentucky. The program objectives are: (1) to reduce morbidity and mortality from cancer by transfer of cancer information from the research community to practicing physicians, health organizations, allied health professionals and others involved in cancer, (2) to provide cancer information to lay public to encourage consumers to take a more active role in early detection and prevention, (3) to coordinate and utilize existing resources to expand the quality and volume of cancer related activities in Kentucky, (4) to enhance communications among health professionals, medical organizations, and others in the area of cancer control, (5) to evaluate existing programs and new program development in order to accomplish objectives more effectively.

Accomplishments: Six community outreach regional offices, each of which is staffed by a regional coordinator and a secretary, serve as resources and facilitators for cancer related information, education and referral. The coordinators work with interdisciplinary, voluntary district cancer councils which have a combined membership of 180 physicians, nurses health care administrators, social workers, patients, and interested lay persons. Besides tumor conferences and tumor boards that have been held in five major areas, physicians also participate in continuing education programs, the educational brochure series, and treatable cancer symposiums. Nursing continuing education has been offered to 200 nurses, and 17 community hospitals in Eastern Kentucky have participated in the cancer educational materials project. Cancer information is provided to physicians and nurses on request through the Cancer Learning Center. Psycho-social programs for coping with cancer have been offered, and the hospice program development has been given to 20 different groups in Eastern Kentucky with over 300 persons in attendance.

The Network continues to provide a catalogue of patient and public cancer educational materials to hospitals, health departments, and physicians' offices around the state. The Network staff have published four educational booklets on cancer related topics including "Myths and Misconceptions About Cancer", "Self-Examination After Breast Cancer Surgery", "You and Your Cancer", and "You and Cancer Chemotherapy". Another major effort of the outreach has been breast self-exam instruction which was offered to 500 women throughout the state. Other public cancer education programs including smoking awareness, general cancer information, nuclear waste, breast cancer, and teaching the sick child have been offered in the various communities.

Plans: One major plan for the forthcoming year is to begin developing a statewide program in collaboration with the University of Louisville, community hospitals, and physicians groups. Initial focus for collaboration will be in the area of a tumor registry and protocol activities. Secondly, additional tumor boards and conferences will be developed within the communities on treatable cancers. With the construction of a new clinical facility for cancer care, major activities

Program Director: Margaret E. Holmes, Ph.D.

to further develop protocol research and protocol treatment with the communities will be initiated. The program plans to strengthen community awareness by campaigns in the school systems and through public television programs.

Grant 22190: A Pilot Demonstration Detection Program - Community
Cancer Corporation of Luzerne County

From 09/30/78 to 08/31/81

FY 81: 0 (Ann. \$215,562)

Dr. V. F. Greco, Community Cancer Corporation of Luzerne County,
Wilkes-Barre, Pennsylvania 18703

Objectives: The initial goals included the training of Nurse Clinicians to conduct cancer screenings under the supervision of a physician and the evaluation of their performance in the conduct of the relevant examinations. Secondly, the project anticipated the screening of approximately 5000 persons over the age of 40 during the 02 and 03 years of grant support. Additionally, the established goals were to study variables in patient participation and to ascertain the degree to which nurse-conducted screenings are acceptable to the area physicians. The overall plan was to examine the validity and reliability of this form of cancer screening. Subsequently, their plans were modified to include the analysis of costs, and the development of programmatic self-support by the community. The long-range goal encompassed planning for additional epidemiological research in future years, as well as provisions to support the introduction of a single county tumor registry.

Accomplishments: Two hospital-based clinics became operational during September/October 1979 in Hazelton and Wilkes-Barre. The clinics were staffed by specially trained Nurse Clinicians who under physician supervision performed cancer screening examinations for seven body sites. Those encompassed the skin, mouth, throat, rectum, prostate, breast and cervix. Over the three year term of the grant, the screening effort reached 6500 persons and confirmed 50 malignancies. In another twenty-five percent, there were suspicions of cancer or other life-threatening disease. The cases and those with suspicion of cancer or other diseases were then referred back to their primary physician for additional follow-up and treatment. Initially, each person responding to the screening invitation was asked to complete a questionnaire designed to elicit screenee response on the acceptability of the clinic program and the recruitment methodology. While subsequent changes in recruiting lead to an elimination of the recruitment evaluation, it was concluded from the overall screenee response that the program was fully acceptable to the citizens of the Luzerne Community. A second questionnaire went to physicians with the aim of assessing whether the role played by the Nurse Clinician was acceptable to them. The results of the physician survey are being currently analyzed.

The major accomplishment included the attracting of community resources for continuation of the program. Contributors were the United Way and a group of volunteers concerned about cancer and cancer prevention. Other tangible benefits to the community were outreach programs in the form of major seminars conducted for physicians and related health professionals. Also, teaching programs were aired using both closed-circuit and the public broadcast media. Generally, the programs were regarded as successful and fully acceptable to the lay and professional/public of Hazelton/Wilkes-Barre areas.

Program Director: Robert T. Bowser, Ph.D.

Plans: Research for the coming year will include work toward a single county tumor registry, as well as efforts to find resources for a continuation of this program.

Grant 22219: Resources that Aid the Recovery of Cancer Patients

From 09/01/80 to 09/01/81

FY 81: 0 (Ann. \$174,000)

Dr. Theresa F. Rogers, Columbia University, New York, New York 10027

Objectives: The aim of this research is to describe the recovery experiences of patients who have had a mastectomy or permanent colostomy and to analyze the effects on recovery of social support from health professionals and from family, friends, and co-workers, as well as from informational resources. In addition, the influence of four medical factors will be examined: length of hospital stay, extent of surgery, one- versus two-stage surgical procedure, and adjuvant therapy. Data for this research are available from one-hour interviews with 652 mastectomy patients and 161 permanent colostomy patients that were conducted with previous support from the National Cancer Institute.

Accomplishments: Analysis is underway to describe the extent to which the resources noted above are available to patients; to assess the relative importance of each, and to delineate how different kinds of treatment affect the speed and extent of recovery. Our research findings to date focus on mastectomy patients and may be qualified by subsequent analysis.

1. Most women report that they did not receive emotional support from medical professionals. Only one-quarter received such help from their surgeons, and one-third from their family physician or gynecologist. Fewer than one in four indicated support from nurses, social workers or other physicians.
2. In contrast, almost all women received emotional support from family and friends. Nine in 10 had a confidant, and 70 percent said the people close to them understood their feelings.
3. Forty percent of the mastectomy patients did not have as much information as they wanted. One-third named their surgeon as their best source of information.
4. Recovery from mastectomy surgery varies by age. On virtually all measures used to assess the emotional consequences of breast cancer, younger women report more problems, especially more fear of recurrence and more concern about disfigurement. However, they do not fare badly in terms of objective recovery--they resume their usual activities sooner than older women do.
5. For women in their 40's and 50's, a good marriage helps to reduce fear of recurrence.
6. Especially for women over 60, chemotherapy poses an obstacle to recovery. Although younger women are more likely to have undergone this kind of treatment, women over 60 who receive it take far longer to return to their usual activities.

Program Director: Rosemary Yancik, Ph.D.

Grant CA 22367: Processing of Nuclear RNA in Colon Carcinogenesis

From: 06/01/78 to 05/31/81

FY 81: -0- (Ann. \$59,456)

Dr. Leonard H. Augenlicht, Sloan-Kettering Institute for Cancer Research,
145 Boston Post Road, Rye, New York 10380

Objectives: We have sought to clone nucleic acid sequences which are differentially expressed in a dimethylhydrazine-induced mouse colon carcinoma. These pure cloned sequences can be used to study the role that changes in gene expression play in carcinogenesis at the molecular level and the mechanisms by which they are brought about, questions that have been difficult to approach experimentally due to the relatively small number of alterations as compared to the total complexity of the mRNA population in eukaryotic cells.

Accomplishments: We have cloned in *E. coli* the population of poly A⁺ cytoplasmic RNA sequences expressed in a dimethylhydrazine-induced transplantable mouse colon tumor. These clones were extensively screened with ³²P-cDNA made from the poly classified each cloned sequence as to its abundance in these two tissues. Of 378 clones screened with both populations, 55 (15%) exhibit changes in expression in the tumor as compared to the normal colon. Eight sequences (2%) exhibit pronounced changes: 7 are detectable in the normal tissue but are abundant in the tumor, while 1 shows the opposite change.

The clones have also been screened with cDNA of liver and kidney; several interesting patterns emerge. Seventy-nine percent of the sequences show no evidence for tissue specific expression. Fifteen sequences characteristic of the colon continue to be expressed in the tumor, while of those sequences which do markedly decrease in the tumor, most are again characteristic of the colon. Finally, 9/10 sequences whose expression increases from low abundance in the normal to high abundance in the tumor are also expressed at high levels in the liver and kidney, while those that show more modest increases are absent from the other 2 normal tissues.

Plans: We are using a number of the cloned sequences as probes to study the kinetics of change in expression and appearance of new cell phenotypes in the colon during dimethylhydrazine treatment and the involvement of genomic sequence rearrangement and methylation in the altered expression. In addition, the pattern of change in expression in mouse NIH 3T3 cells transformed with human colon tumor DNA is being investigated.

Publications:

Augenlicht, L.H.: Digestion Products of Nuclear Ribonucleoprotein. In The Cell Nucleus, H. Busch, Ed. New York, Academic Press, in press, 1981.

Program Director: Vincent J. Cairolì, Ph.D.

From: 08/01/77 to 07/31/81

FY 81: -0- (Ann. \$48,950)

Dr. M.A. Correia, University of California, San Francisco School of Medicine,
1120 HSW, San Francisco, CA 94143

Objectives: The goals of this research project have been to delineate the possible role of colonic cytochrome P-450-dependent mixed function oxidases (MFO) in dimethylhydrazine (DMH)-induced colon carcinogenesis and to determine whether the system undergoes any functional alterations during induction of chemical carcinogenesis. Our studies have suggested that jejunio-ileal resection of rats greatly increases cytochrome P-450-dependent MFO activity of the colonic mucosa possibly by increasing its access to nutrients, biliary constituents and/or physiological modulators such as gastrin. In the past year, we have investigated whether such increased access of the colonic mucosa to duodenal contents affect (i) DMH-induced colon carcinogenesis and (ii) colonic microsomal cytochrome P-450-dependent-MFO activity.

Accomplishments: Male Sprague Dawley rats (N=16) underwent (70%) jejunio-ileal resection followed by anastomosis of the proximal duodenum to distal ileum. An equal number underwent a sham-operation and served as controls. Animals were given free access to food and water and allowed to recover for a couple of weeks before being fed a semisynthetic, iron-supplemented diet. Eight animals in each group were fed β -naphthoflavone (β -NF), an inducer of intestinal cytochrome P-450 in the diet. They were then injected with 15 weekly subcutaneous injections of DMH (20 mg/kg), and maintained on the respective diets for the next 35 weeks until sacrifice. On sacrifice, the incidence and frequency of tumors in each group of rats was examined, and intestinal and colonic cytochrome P-450 (c) reductase and cytochrome P-450-dependent aryl hydrocarbon hydroxylase activity were determined using benzpyrene as the substrate.

As expected, colonic cytochrome P450-dependent enzyme activities were enhanced in resected rats than in correspondingly treated sham rats. The studies also suggest that enhanced dietary access of inducers of cytochrome P-450 not only increase cytochrome P-450-dependent MFO activity in colonic mucosa and in colonic tumors, but apparently exacerbate colonic carcinogenesis as well, as indicated by the increased number of DMH-induced tumors in β -NF-pretreated rats. However, the mechanistic interpretation of this finding warrants caution, given the poor survival of these rats on DMH-treatment.

Plans: These studies are currently being repeated with increased numbers of experimental rats to overcome statistical limitations due to poor survival.

In separate experiments we plan to evaluate the role of selenium deficiency in DMH-induced colon carcinogenesis.

Publications: None.

Program Director: Vincent J. Cairoli, Ph.D.

Grant CA 22370: Antigenic Stimulus in Human Colon Carcinoma Immunity

From: 01/01/77 to 05/31/82

FY 81: \$122,286 (est.)

Dr. Barry D. Kahan, The University of Texas Health Science Center at Houston
Medical School, 6431 Fannin Street, Houston, Texas 77030

Objectives: The objectives of this project are to chemically and immunologically identify cell surface antigens characteristic of colonic neoplasia, and to identify signals and/or receptors determining organoid differentiation. The biology of human colon cancer is being studied using reference cell lines and nine clones of one line, LS174T. Plasma membranes of LS174T cells are prepared and either combined with or incorporated into multilamellar vesicles (MLV) (liposomes) to study the efficacy of antigen presentation in humoral immune response to cell surface antigenic components. Polyclonal and monoclonal heteroantisera to cell surface antigens are being evaluated.

Accomplishments: Plasma membranes of LS174T human colon cancer cells were either co-incubated with negatively charged MLVs prepared from 7:2:1 molar ratios of choline, cholesterol, and phosphatidic acid in the presence of 8mM calcium chloride or used in the preparation of MLVs. Rabbits were immunized for each antigen group and sera screened by indirect immunofluorescence for antibodies reacting against LS174T cells. The MLV plus membrane preparation produced higher titers of antibodies which appeared earlier than with the other antigen preparations. A radioimmune assay (RIA) confirmed these results which indicate that the presentation of antigens on the surface of liposomes provides the best immunogenic configuration for generating antibody activity against cell surface antigenic components. Nine sub-clones of human colon cancer cells, LS174T, have been isolated, subcloned, and characterized for: cell and colony morphology; carcinoembryonic antigen (CEA) and mucin production; tumor growth kinetics in nude mice; colony formation in soft agar; population doubling time; allelic isozymes (genetic signature) and isozyme gene expression; nuclear magnetic resonance (NMR) relaxation times of water protons; and organoid growth in hollow fiber culture. Cell and colony morphology, population doubling times, NMR water proton mobility, allozyme phenotypes, and the expression of isozymes which are variably expressed in different tissues, did not vary among the clones and parent line. Properties which reflect the malignant nature of the cell line did vary among the clones. Three of the clones tested have produced organoid growth on the perfused hollow fiber culture system. Clonal analysis of a human colon tumor cell line indicates that the parent line represents a composite of several cell lineages that may reflect variation which occurs during tumor progression and are preserved and amplified during in vitro culture.

Plans: We plan to immunize mice with colon cancer cell membranes mixed with MLV liposomes. These studies will form the basis for production of mouse monoclonal antibodies to cell surface antigenic components of human colon cancer cells grown either in monolayer or as organoid structures in hollow fiber culture. The latter antigenic preparation will be used to identify surface antigens associated with differentiated growth. The relationship between tumor growth rate and CEA shedding will be examined.

Publications: Rutzky, L.P., Kay, C., Siciliano, M.J., Chao, M., and Kahan, B.D.: Longitudinal Karyotype and Genetic Signature Analysis of Cultured Human Adenocarcinoma Cell Lines LS180 and LS174T. Cancer Res., 40:1443-1448, 1980.

Program Director: Vincent J. Cairoli, Ph.D.

From: 08/01/78 to 07/31/81

FY 81: -0- (Ann. \$57,512)

Dr. Robert Yonemoto, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010

Objectives: A feasibility study using transfer factor (TF) from either "cured" colorectal carcinoma, "cured" breast carcinoma, or normal controls, to treat post-operative colorectal cancer patients less than 3 years free of disease, and patients with recurrent disease is in progress. The presence of serum blocking factors (SBF) will be assessed according to stage, disease-free interval and tumor burden using the leukocyte adherence inhibition (LAI) assay. The effects of TF on LAI and SBF will be assessed. It is hoped that the studies will explain the mode of action and the specificity of TF. A vertical study in patients undergoing curative resection of colorectal carcinoma will be conducted. Pre- and postoperative serial LAI assays will be correlated with stage of disease, tumor burden, and CEA.

Accomplishments: The HT-29 cell line has been used to isolate antigens from KCl extracts of cultured cells and from spent culture medium. The spent medium was concentrated and tested against the sera of colon cancer patients, non-colon cancer patients and normal donors by the micro-complement fixation test. The data suggest that the HT-29 cell line adapted to grow in chemically defined medium (CDM) synthesized a carcinoma-associated antigen which was released in the spent CSM. Use of this substance as antigen in the LAI system shows promise. Ascites fluid has also been used as a source of tumor-associated antigen (TAA). The ultrafiltrate was tested for presence of TAA by the enzyme-linked immunosorbent assay (ELISA). This material has been partially purified and one peak tested for antigenic activity. Further purification is being carried out using lectin column chromatography. An automated microslide LAI has been developed which provides for improved reproducibility, elimination of subjectivity and rapidity. To date, 66 patients with colorectal cancer have been studied as well as additional patients with other malignancies and healthy controls.

Plans: Patients will continue to be entered into both the vertical and horizontal studies and the specificity study of TF will be completed. Improvement of the LAI assay using other sources of TAA, such as ascites, will be explored and an ELISA will be developed further to detect IgG and IgM antibodies in colon cancer patient's serum. A correlation between TF administration and in vitro assays will be sought.

Publications:

Chee, D.O., Gupta, R.K., and Morton, D.L.: Presence of a carcinoma-associated antigen(s) in the spent chemically defined medium of a human colon carcinoma cell line. J. Surg. Oncol., 13:45-51, 1980.

Program Director: Vincent J. Cairoli, Ph.D.

From: 08/01/78 to 07/31/81

FY 81: -0- (Ann. \$57,203)

Dr. Lidia C. Boffa, Rockefeller University, 1230 York Avenue, New York, NY 10021

Objectives: The primary aim is to isolate and characterize a cyanate metabolite which specifically inhibits protein synthesis in colonic adenocarcinoma cells, without appreciable effect on protein synthesis in normal cells. The mechanism of action of the metabolite will be investigated, with emphasis on its effects on amino acid transport, activation, protein chain initiation, elongation, and accessory postsynthetic modifications. The relationship between cyanate sensitivity and the expression of the malignant phenotype will be investigated in cells transformed by chemical carcinogens and temperature-sensitive oncogenic viruses.

Accomplishments: Cyanate has been shown to selectively inhibit protein synthesis in primary colonic tumors induced by dimethylhydrazine (MDH), and in transplantable murine colonic tumors T36 and T38. Normal cells were not inhibited under these conditions, but fibroblasts which are normally insensitive to cyanate became sensitive after transformation by Rous Sarcoma virus. T36 cells or human colonic tumor cells (HT-29) are not sensitive to cyanate in culture, unless the cyanate is activated by a cytochrome P-450 system. Conditions for the induction of an active hepatic cytochrome P-450 system have been developed using Arochlor 1254 or phenobarbital as inducers. Methods for the generation of the cyanate metabolite in vitro and for testing its effect on tumor cells in culture were also developed. The correlation between malignancy and cyanate sensitivity was probed using sodium butyrate to suppress the malignant phenotype. Butyrate-treated tumor cells lose their sensitivity to the cyanate metabolite. We have found that butyrate arrests the phosphorylation of histones H1 and H2A we believe to be essential for cell cycle progression.

The formation of the tumor inhibitory cyanate metabolite was shown to be enzymatically catalyzed. The product is unstable, but can be trapped using N-4 nitrophenyl-N-n-propylamine. A requirement for peroxidation is suggested by the inhibitory effects of catalase in the reaction system, but superoxide dismutase does not destroy the inhibitory effect. Oral cyanate was shown to inhibit tumor growth and prolong the survival of mice-bearing colonic adenocarcinoma T36.

Plans: The structure of the cyanate metabolite will be investigated using ^{14}C -cyanate and its conversion to other compounds by the cytochrome P-450 system. The product will be tested for its mechanism of action on the protein biosynthetic reactions. The combined effect of cyanate plus an inducer of cytochrome p-450 (phenobarbital) will be tested on transplantable colon tumors.

Publications:

Boffa, L.C., Kozak, S., and Allfrey, V.G.: Activation of Sodium Cyanate for Selective Inhibition of Protein Synthesis in Cultured Tumor Cells. *Cancer Res.*, 41: 60-66, 1981.

Allfrey, V.G., Kozak, S., and Boffa, L.C.: Selective Inhibition of Protein Synthesis in Colonic Carcinoma. In Falk Symposium #36, R.A. Malt, Ed., in press, 1981.

Program Director: Vincent J. Cairolì, Ph.D.

Grant 22460: Assessment of Techniques for Endometrial Cancer Detection

From 02/01/80 to 01/29/82

FY 81: \$69,835

Dr. Marluce Bibbo, University of Chicago, Chicago, Illinois 60637

Objectives: It is the objective of this study to evaluate in an academic environment and in the community the relative efficacy of cytologic and microhistologic techniques for the detection of endometrial cancer and its precursors. Three techniques, namely, the endometrial aspiration (Vakutage), the endocervical aspiration and the routine vaginal, ectocervical, and endocervical (VCE) cytologic smears will be assessed. This study will have a significant impact on defining efficacy for a health screening program and the early detection of endometrial carcinoma and its precursors.

Accomplishments: In the preparatory stage, which spanned the first four months of the study, the clinicians were instructed in the use of the above three techniques. Of 181 cases, 178, or 98%, of the VCE smears, 172, or 95%, of the endocervical aspirates, and 158, or 87%, of the Vakutage specimens were adequate. In the main stage of the study, 670 patients so far fulfilled the criteria for admission to the study. Six hundred sixty-three, or 99%, of the VCE smears, 658, or 98%, of the endocervical aspirates and 628, or 93%, of the Vakutage specimens were adequate. The data collected so far comprise 75 confirmed cases of adenocarcinoma, 5 of mixed mesodermal tumors, 5 of mixed adenosquamous carcinoma, 15 of atypical adenomatous hyperplasia, 75 of adenomatous hyperplasia, 40 of cystic hyperplasia and 32 of endometrial polyps. 93% of the cases of malignancy were detected by the Vakutage sample, but only 67% by the VCE smears and 68% by the endocervical aspirate. The Vakutage sampling technique was the most accurate method in the detection of endometrial hyperplasias (85% diagnostic accuracy for cystic hyperplasias and 88% for adenomatous hyperplasias versus 10% and 13% for VCE smears or endocervical aspirate). In the preparatory stage of the outreach program, the yield of the three samples was similar to the University of Chicago. The evaluation of fixation of eight carrier fixatives showed that a mixture of equal parts of 95% ethanol and 10% formalin gives the best fixation for endometrial aspirates which have to be transported to the University of Chicago for processing.

Plans: We plan to continue the main stage of the project at the University of Chicago hospitals and the community. This will require 10 additional months. Detection rates of endometrial cancer and its precursors will be assessed.

Publications: Bibbo, M., Reale, F., Reale, J., Azizi, F., Bartels, P., Wied, G., Haff, S., Herbst, A.: Assessment of three sampling techniques to detect endometrial cancer and its precursors: A preliminary report. Acta Cytol. 23:353-359, 1979.

Program Director: Robert T. Bowser, Ph.D.

From 06/01/78 to 05/31/81

FY 81: \$0 (Ann. \$58,308)

Dr. J.M.S. Caruthers and M.A. Bonneville, Department of M.C.D. Biology,
Boulder, Colorado, 80309

Objectives: The primary objective of this project is to document more completely the biochemical changes initiating and/or accompanying morphological changes thought to be critical in the transition from reversible to irreversible tumorigenesis in rat urothelium. It has been suggested that the formation of microvillar projections at the luminal surface and the appearance of an extensive glycocalyx describe the stage in experimental bladder cancer development that is committed to progression into carcinogenesis. Our previous study indicated that in a fashion similar to morphological studies, certain biochemical parameters also showed initially reversible changes and later irreversible changes.

Our present study is focused on biochemical events which might ultimately be expressed as the observed morphological changes. Male Sprague-Dawley rats were given a subcarcinogenic dose of MNU (N-methyl-N-nitrosourea) followed by daily feedings of saccharin (5%) of diet). Ninety eight rats were placed into seven groups and experimentally induced carcinogenesis was allowed to progress for 4, 10, 12, 14, 16, 20, and 30 weeks. In order to observe a possible recovery phase, one half of the rats was sacrificed after each time interval, while the other half was returned to a regular diet. A control group was not treated with MNU, but was put on the saccharin diet to study possible effects of this agent alone.

One of the major morphological changes found in the plasma membrane of the cancerous urothelium most probably reflects involvement of the Golgi complex. The appearance of the extensive glycocalyx can be visualized electron microscopically. This apparent enrichment in carbohydrate content along the external urothelial surface probably mirrors enhancement in enzyme activities that are normally associated with the Golgi complex, but are possibly transferred to the altered plasma membrane surface in (pre) carcinogenic cells. We are presently determining thiamine pyrophosphatase, sialyltransferase and galactosyl transferase activities in isolated fractions of the different experimental stages in urothelial carcinogenesis. Since the Golgi complex also appears to be involved in processing fusiform vesicles destined for plasma membrane replacement, information may be obtained to understand the basic biochemical changes underlying the disappearance of AUM structure. We will attempt to correlate these changes in membrane morphology with the disappearance of the 24,000 dalton subunit from the luminal plasma membrane. Our immediate plans include attempts to specify the critical period determining whether or not a cell continues into carcinogenicity.

Program Director: William E. Straile, Ph.D.

Publications in the past year

Caruthers, J.M.S. and Bonneville, M.A.: Interaction of Antibodies to Sheep Urothelial Plaque Regions with the Luminal Plasma Membranes of other Mammals. Urol. Res. 8: 129, 1980.

Caruthers, J.M.S. and Bonneville, M.A.: Luminal Plasma Membrane Alterations in Bladder Cancer. Invest. Urol. 17: 364, 1980.

Manuscript in preparation

Caruthers, J.M.S., McAuliffe, J.D. and Bonneville, M.A.: Morphological and Biochemical Parameters in the Progression of Rat Urothelial Carcinogenesis. 1981.

Abstract

Bonneville, M.A. and Caruthers, J.M.S.: Correlation of Biochemical and Morphological changes during Rat Urinary Bladder Carcinogenesis. Presented at the National Bladder Cancer Project Investigators Workshop, Sarasota, Florida. 1980.

Grant 22582: Exocrine Pancreatic Proteins in Pancreatic Cancer

From 08/01/74 to 09/29/81

FY 81: 0 (Ann. \$51,189)

Dr. George Scheele, Department of Cell Biology, Rockefeller University,
1230 York Avenue, New York, New York 10021

Objectives: The overall objective of this project is to characterize the proteins which appear in human pancreatic juice in health and disease. Specific objectives are to: (a) develop reliable techniques for the separation and analysis of normal exocrine proteins contained in human pancreatic juice; (b) characterize each by isoelectric point and apparent molecular weight; (c) identify these proteins by actual or potential enzyme activities; (d) analyze for the appearance of abnormal proteins in pancreatic juice obtained from patients with pancreatic cancer and pancreatitis and (e) ultimately determine if additional proteins represent specific biochemical markers of these disease states.

Accomplishments: Addition of 6M urea to the pancreatic juice samples and 8M urea to the isoelectric focusing procedure used in our two dimensional separations of proteins prevented autoactivation of human pancreatic proteases and allowed the successful separation of 19 discrete proteins. These proteins have been characterized in detail according to specific objectives (b) and (c) described above. We have recently used the two dimensional gel procedure to analyze samples of pure pancreatic juice obtained from 10 normal subjects, 8 patients with chronic pancreatitis and 6 patients with pancreatic cancer. A new silver stain, 100 times more sensitive than Coomassie blue, was used to stain for proteins. Samples of pancreatic juice from patients with disease showed a number of additional proteins not observed in juice from normal individuals. Other than serum albumin we have not been able, to date, to identify these additional proteins. Furthermore, from the two dimensional pattern of these additional proteins, we could not clearly distinguish chronic pancreatitis from pancreatic cancer.

In the past six months we have embarked on a new direction in order to ultimately identify unique antigens which may be associated with pancreatic disease states, particularly that of pancreatic cancer. We have set up tissue culture facilities and somatic cell fusion techniques to produce monoclonal antibodies directed against surface antigens associated with pancreatic cancer cells (Capan 2 cells obtained from Dr. J. Fogh of the Sloan-Kettering Institute). To date, three fusions have been conducted and we are presently assaying hybridoma media for antibodies specifically directed toward antigens expressed by Capan 2 cells.

Plans: Our immediate plans are to raise a number of monoclonal antibodies directed specifically toward antigens uniquely associated with pancreatic cancer cells. Indicator cell binding studies and immunofluorescence techniques will be used to characterize the reactivity of individual antibodies toward (a) plasmalemmal elements of pancreatic carcinoma cells vs. normal human pancreatic cells (acinar vs. ductal cells) and (b) a number of normal human tissues as well as a variety of human carcinomas. Monoclonal antibodies with the specificity described above will be used to (1) characterize corresponding antigens by isoelectric

Program Director: William E. Straile, Ph.D.

point and apparent molecular weight and (2) identify antigens shed into a variety of human body fluids including pancreatic juice by competition binding studies and two dimensional gel electrophoresis. In addition, serum components appearing in juice samples from patients with pancreatic disease will be identified after separation by two dimensional gel electrophoresis using monospecific antibodies directed against human serum proteins.

Publications:

Bieger, W., and Scheele, G.: A sensitive and specific assay for elastase activity using $[^3\text{H}]$ a elastin as substrate. Anal. Biochem., 104, 239-246, 1980.

Bieger, W., and Scheele, G.: Two-dimensional isoelectric focusing/sodium dodecyl sulfate gel electrophoresis of protein mixtures containing active or potentially active proteases. Analysis of human exocrine pancreatic proteins. Anal. Biochem., 109, 222-230, 1980.

Scheele, G., Bartelt, D., and Bieger, W.: Characterization of human exocrine pancreatic proteins by two dimensional isoelectric focusing/sodium dodecyl sulfate gel electrophoresis. Gastroenterology, 80, 461-473, 1981.

Grant 22682: An In Vitro Model of Pancreas Carcinogenesis

From 08/01/78 to 07/31/81

FY 81: 0 (Ann. \$45,402)

Ismail Parsa, M.D., State University of New York, Downstate Medical Center,
Brooklyn, New York 11203

Objectives: An in vitro model of human pancreas carcinogenesis using organ-cultured adult human pancreas was developed using DMNA or MNU to induce pancreatic carcinoma. It is expected to study the modulation of cell surface markers of pancreatic epithelium during carcinogenesis in this in vitro model. Specifically, it is expected to develop monoclonal antibodies to cell surface determinants on pancreas cell types and to examine the modification of these markers at various phases of carcinogenesis.

Accomplishments: Monoclonal antibodies to various cell surface markers of normal pancreas and organ-cultured pancreas exposed to MNU will be produced. Antibodies to normal acinar, centroacinar, and ductular epithelium will be obtained. It is expected to determine the cell surface distribution of these determinants on normal acinar, centroacinar and ductal epithelium in normal pancreas and any alteration in marker density on these cells in pancreas exposed to MNU. Definition is expected to specific patterns of alteration in progenitor cells of carcinoma.

Plans: It is planned to use hybridoma cells for the production of antibody by fusion of mouse myeloma with splenocytes of mice immunized against normal or MNU-treated pancreas. Monoclonal antibodies will be tested by indirect fluorescence technique, and ultimately a battery of antibodies specific for surface determinants of each cell type will allow monitoring of the modulation of cell surface markers during carcinogenesis and also delineation of each phase in this process.

Publications:

Parsa, I., Marsh, W.H. and Sutton, A.L.: An in vitro model of pancreas carcinoma: N-nitroso-bis(2hydroxy propyl)amine effects. Cancer Letters 9:1-6, 1980.

Parsa, I., Marsh, W.H., Sutton, A.L. and Butt, K.M.H.: Effects of dimethylnitrosamine on organ-cultured adult human pancreas. Am. J. Pathol. 102:403-411, 1981.

Parsa, I., Marsh, W.H. and Sutton, A.L.: An in vitro model of human pancreas carcinogenesis: Effects of nitroso compounds. Cancer 47:1543-1551, 1981.

Program Director: William E. Straile, Ph.D.

From 04/01/79 to 06/30/82

FY 81: \$907,553 est.

Stephen K. Carter, M.D., Northern California Cancer Program, 1801 Page Mill Road, Palo Alto, California 94304

Objectives: Development of a comprehensive cancer control program for Northern California and Northwestern Nevada through the development of: integrated service areas (ISA's); intervention programs in education, rehabilitation, clinical trials outreach, evaluation, prevention, communications; and a DES demonstration project.

Accomplishments: A Cancer Control Planning Committee has been formed, which meets quarterly and includes representatives from appropriate disciplines and organizations, including integrated service areas (ISA's). Nine ISA's are now in existence, in various stages of development with several sources of financial support. A manual for ISA development and organization is being written. An ISA Directors Committee has been formed and holds bimonthly meetings. The NCOG-Outreach program was successfully developed and receives separate funding. Rehabilitation activities include rehabilitation guidelines, vocational rehabilitation and planning of regional rehabilitation conferences for community hospitals. The DES Project, completed in 24 months, expanded to ISA's. Follow-up activities with DES Action-San Francisco and their national network has continued. Other organizational activities included: demographics data collection for the NCCP service area by county and by ISA; a traveling oncology program; review of patient education materials; development of smoking cessation project; individual evaluation plans for all activities; nutrition booklet with prevention orientation; Chinese health and education study; completion of cancer-related occupational health materials and agencies; second draft of tumor registry manual; and completion of a cancer services index for San Mateo County. Communications included publication of an improved regionwide monthly newsletter and calendar for health professionals; editing "What's New in Cancer Care"; partial implementation of computerized mailing system; and other information activities. Accomplishments resulting from individual ISA activities include, but are not limited to: needs and resource assessments; head and neck and colo-rectal pre-treatment conferences; smoking cessation project; newsletters; participation in NCOG-Outreach; professional education programs; development and revision of cancer patient services indexes for each community; laryngectomy emergency tapes (LET); and hospice coordination.

Plans: Completion of a Tumor Registry Manual for ISA's and pilot project of its utilization; continued updating of catalog of data/resources; continued publication of newsletter, calendar, and "What's New in Cancer Care"; completion of computerized regionwide mail list; continued development of ISA's continued implementation of rehabilitation and educational activities; completion of cancer services indexes; continued participation in local hospice activities; expansion of NCOG-Outreach; provision of technical expertise in rehabilitation, education, outreach, prevention, and communications to ISA's and other participating organizations; publication and distribution of nutrition pamphlet; regional rehabilitation conference for community hospitals.

Program Director: Carlos E. Caban, Ph.D.

Grant CA 22842: Cancer Control Developmental and Support Grant

From 12/01/77 - 03/31/81

FY 81: 0 (Ann. \$357,000)

Richard A. Gams, M.D., University of Alabama in Birmingham, Comprehensive Cancer Center, Birmingham, Alabama 35294

Objectives: Goals of this project were to maintain and continue development of three Cancer Control programs: TOUCH, an oncology self-help program; Ministry to the Cancer Patient, an educational program for Alabama clergy; and tumor boards in several cities. In addition, we offered a supervised practicum and internship for students completing a Master's Degree in Rehabilitation Counseling.

Accomplishments: TOUCH is established in nine Alabama communities, one city in Pennsylvania and one in Louisiana. We surveyed the Alabama TOUCH participants in 1980 and our findings were similar to those of the 1978 survey. Reported benefits of the program included sharing with others who had similar problems, learning more about cancer, improving communications skills, and learning new coping mechanisms. In addition, we found the Reissman "Helper-Therapy" principle operating: those TOUCH participants who visited and counseled other patients reported more benefits than those who did not visit others. Ministry to the Cancer Patient is held each May and October and between 15 and 20 clergy attend each training session. Seventy-six have completed the four day lecture and clinical experience. Monthly tumor conferences are held in Tuscaloosa, and Tuskegee, Alabama and Columbus, Missouri. Tumor boards are also held approximately six times per year in Montgomery and Anniston, Alabama and Atlanta, Georgia at our cooperating CHOP Hospital.

Plans: We are waiting for new Cancer Control Guidelines; when we receive them we will consider submitting a grant application.

Publications:

Maisiak, R., Cain, M., Henke, C., Josof, L. "Evaluation of TOUCH: An Oncology Self-Help Group," Oncology Nursing Forum, Summer, 1981.

Lebow, J., Maisiak, R., Soong, S-J., Sanders, E., Cain, M. "Rehabilitation Counseling Needs of Cancer Patients", Rehabilitation Counseling Bulletin.

Program Director: Carlos E. Caban, Ph.D.

From: 09/30/77 to 12/31/80

FY 81: -0- (Ann. \$56,130)

Dr. Brahma P. Sani, Southern Research Institute, 2000 Ninth Avenue South,
Birmingham, AL 35255

Objectives: The overall objective is to understand the significance of the appearance of retinoid-binding proteins in colon carcinogenesis. Quantitative analysis for retinoic acid-binding protein (RABP) in human and experimentally induced primary colon tumors, and in colon segments at different distances from the tumor by a recently standardized rapid and sensitive assay method will be carried out, and the metastatic capabilities of transplantable human tumors in nude mice will be assessed from the appearance of RABP in different tissues on successive days after implantation. The approach may help to develop and to evaluate quantitative biochemical procedures for detection of human large bowel cancer.

Accomplishments: RABP is distinctly present in embryonic colon and lung as well as in experimental murine colon tumors, but is not detected in adult mouse colon or lung. Of the 103 human colon tumors and related specimens analyzed for RABP, 80% contained the binding protein in detectable amounts. RABP was also detected in 3 colon segments about 5 cm away from the tumors, but none of 8 normal colon tissues examined showed binding activity. Like RABP, a dihydrotestosterone-binding protein was detected in 90% of the human colon tumors but was not in normal tissues. The human colon tumor RABP exhibited physicochemical properties similar to RABP from other species. Based on our finding that mercurial-sensitive thiol functions are involved in the binding of the ligand to RABP, a rapid and sensitive assay method for detection and quantitation of RABP has been developed. The lower limit for detection of RABP in transplantable mouse colon tumor 26 corresponds to 0.1 mg extractable protein from the tumor. After subcutaneous implantation in mice, RABP was evident in the lung extracts after the 4th day. Fragments of mouse lungs containing the metastatic tumor foci, after subcutaneous reimplantation in mice, produced tumors which showed RABP levels comparable to those in the original colon tumor. RABP and a cellular retinol-binding protein from colon tumor 26 have been reproducibly purified to homogeneity and partially characterized. The kinetics of cellular uptake of retinoic acid and the formation of [³H] retinoic acid-cytosol RABP in colon tumor 26 have been studied. We have obtained evidence for a plasma membrane RABP that may facilitate the selective transport of retinoic acid by epithelial cells.

Plans: An immunization schedule and a hybridoma antibody production technique for RABP will be developed. Studies on genomic control mechanism of retinoic acid and RABP will be expanded. We will also quantitate RABP, cellular retinol binding protein and dihydrotestosterone-binding protein in human and experimental tumors, and human tumor xenografts in relation to tumorigenesis, tumor progression, invasiveness and metastasis.

Publications:

Sani, B.P. and Banerjee, C.K.: Cellular and Subcellular Uptake of Retinoic Acid and Its Mediation by Retinoic Acid-binding Protein. Ann. N.Y. Acad. Sci., 350: 420-421, 1981.

Program Director: Vincent J. Cairoli, Ph.D.

From: 09/30/77 to 04/30/84

FY 31: \$73,723

Dr. Martin H. Goldrosen, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY

Objectives: The objective of this project is to characterize the role of the local, regional, and systemic immune response in an orthotopically transplanted murine colonic tumor model, and compare and contrast it to a subcutaneous transplant of the same cell line. Specific antitumor immunity will be evaluated in vivo by a Winn neutralization test and in vitro by a micro-leukocyte adherence inhibition assay. The potential role of serum blocking factors and suppressor cells in preventing effector mechanisms from operating and thus promoting primary tumor growth and subsequent metastasis will also be evaluated.

Accomplishments: We have established an animal model of colon cancer based on the procedure of orthotopic transplantation of syngeneic murine MCA-38 colonic tumor cells in the submucosa of the cecum resulting in a "primary" tumor that selectively metastasizes to the regional lymph nodes and liver in 60-70% of animals. Excision studies of the primary tumor revealed that initial seeding and arrest in the liver and mesenteric lymph nodes occurred between the sixth and eighth weeks post-orthotopic transplantation. Transplantation of other syngeneic but nontissue-type related cell lines (B-16 melanoma, T-241 Lewis Sarcoma) in the submucosa of the cecum results in a primary tumor that metastasizes to secondary sites other than the liver suggesting that the pattern of metastases observed with the MCA-38 colonic cell line is due, in part, to unique properties associated with these cells. Thus, this model simulates the natural history of human colonic cancer and is an appropriate animal model to segregate and study local, regional, and systemic immune responses, to understand the relationship between primary colon carcinoma growth and subsequent hepatic metastasis. The presence of tumor associated transplantation antigens on the MCA-38 tumor was extensively documented by three classical tests of transplantation rejection that included concomitant immunity, hyperimmunization and challenge, and tumor excision and challenge. Studies were performed with MCA-38 sensitized spleen cells and mesenteric node cells at effector to target ratios ranging from 100:1 to 1:1. MCA-38 tumor cell neutralization occurred with as little as one sensitized effector cell for every MCA-38 tumor target cell indicating that the Winn neutralization test can be adapted to study the temporal development of the local, regional and systemic immune response in the MCA-38 orthotopic model where there is a paucity of effector cells in some but not all lymphoid organs. In preliminary studies with the micro-LAI in vitro assay, a systemic antitumor response was detected with spleen and peritoneal cells during primary tumor growth, which disappeared when hepatic metastasis began to appear. The specific antitumor response of the Peyer's patches and mesenteric nodes was bisphasic with a transient disappearance of the local, regional specific antitumor response occurring before tumor cell seeding and arrest, and the appearance of microscopic and macroscopic regional lymph node and hepatic metastases. The transient disappearance of the local/regional immune response may play a role in metastases formation. This conclusion can further be strengthened by in vitro LAI studies that more closely define the period of lack of reactivity and the appearance of metastases as well as in vivo studies that support this observation by demonstrating the absence of MCA-38 tumor cell neutralizing ability with Peyer's patches and mesenteric nodes taken during the same time interval.

Program Director: Vincent J. Cairoli, Ph.D.

Plans: To further elucidate the role of local, regional, and systemic immune responses in this animal model of colon cancer. Temporal studies on the development of these responses will determine when sensitization occurs in these compartments, as well as the dynamic changes in tumor mediated immune responses from the latency period to the appearance of metastasis. The simultaneous presence of residual tumor cells in the gut, regional lymph nodes, and liver offers a unique opportunity to determine the direct effect of the immune process upon residual tumor cells. We will further develop an in vitro assay that potentially correlates with the in vivo behavior of colorectal tumors and thus will be useful in monitoring tumor immunity in human colorectal cancer patients.

Publications:

Goldrosen, M.H. Murine Colon Adenocarcinoma: Immunobiology of Metastases. Cancer 45/1223, 1980.

From 06/01/78 to 05/31/81

FY 81: \$0 (Ann. \$33,635)

Dr. Frederick H. Batzold, Department of Biochemistry, Albany Medical College, Albany, New York 12208

Objectives: Studies of prostatic 5 α -reductase are in progress to determine if selective inhibition of this enzyme is a viable therapeutic alternative to conventional endocrine manipulation in the control of abnormal prostatic growth particularly adenocarcinoma. This approach includes the design, the synthesis and evaluation of steroid hormone analogs as inhibitors of rat prostatic 5 α -reductase and that derived from the Dunning R-3327 tumor. Structure-activity studies suggest that steroid analogs can be designed which are potent reductase inhibitors but are devoid of androgenic activity and resistant to rapid metabolic inactivation by prostatic tissue.

Accomplishments: The results obtained in the investigation indicate that the steroid nucleus can tolerate a significant number of structural modifications and not severely compromise binding to prostatic 5 α -reductase. The A and B rings of the steroid nucleus can be substituted with non-bulky groups without loss of binding. Selected modifications at C-17 can enhance inhibitory activity, abolish androgenic activity and impart in vivo activity. Appropriate functionalization at C-2 can render androgenic compounds hormonally inactive whereas halogenation at C-4 maintains enzymatic binding and prevents 5 α -reduction to inactive products. Thus, potent inhibitors of 5 α -reductase can be realized which are not substrates and are devoid of androgenic activity. All analogs studied so far which inhibit rat ventral prostatic 5 α -reductase also inhibit the enzyme from the R-3327 tumor; however in vitro inhibitory action does not correlate with in vivo activity in suppressing prostatic growth. The R-3327 tumor 5 α -reductase transforms testosterone at one third the rate of ventral prostate; however this diminished activity does not hold for progesterone processing. This suggests more than one species of reductase exist in tumor tissue. Kinetic inhibition studies with ventral prostate are also suggestive that multiple forms of reductase are present but differ from those in tumor tissue. Taken together these studies demonstrate that selective inhibitors of prostatic 5 α -reductase can be realized for in vivo application to assess the therapeutic potential of 5 α -reductase inhibition.

Plans: The future thrust of this project will be devoted to the preparation of steroid analogs containing multiple modifications, as guided by our previous studies, which will be potent reductase inhibitors for in vivo evaluation on prostatic growth. Those compounds exhibiting in vivo activity will be studied in detail with respect to mechanism of action. These evaluations will include ability to inhibit prostatic 5 α -reductase in vivo, effects in DNA and RNA synthesis, and effects on LH release.

Publications:

Batzold, F. H.: Approaches to Prostatic 5 α -Reductase Inhibitors. In: The Prostatic Cell, Alan R. Liss, Inc. (In press).

Program Director: Andrew Chiarodo, Ph.D.

Grant 23055: Biology of Transplantable Pancreatic Carcinoma of Rat

From 05/01/78 to 04/30/84

FY 81: \$84,104

Janardan K. Reddy, M.D., Department of Pathology, Northwestern University
Medical School, 303 East Chicago Avenue, Chicago, Illinois 60611

Objectives: The objective of the proposed research is to delineate the extent of structural, functional and enzymatic differentiation of a transplantable pancreatic acinar carcinoma of the rat established in our laboratory. Since neoplastic transformation is believed to represent a misprogramming of normal gene expression, it is important to ascertain if differences in the synthesis of specialized exocrine proteins exist among the neoplastic acinar cell population when compared to normal acinar cells. Analysis of cytodifferentiation, secretory protein composition and secretory process of this tumor and other available pancreatic acinar carcinomas as well as delineation of modifying factors should provide basic information regarding the alterations associated with neoplastic transformation and acinar cell differentiation.

Accomplishments: Morphological analysis of transplantable pancreatic acinar carcinoma of the rat has revealed a continuum of cells from those which lack mature secretory granules to cells with abundant well-formed secretory granules. Despite the variation in cytodifferentiation, all neoplastic cells stained positively by immunofluorescence for the six enzymes tested: amylase, lipase, carboxypeptidase A, chymotrypsinogen, trypsinogen and ribonuclease. In addition, hypo-osmotic extracts of the purified secretory granule fraction of the pancreatic carcinoma revealed the enzymic activities of amylase, lipase, trypsin and carboxypeptidase A and B in easily detectable amounts. Ribonuclease, trypsinogen and chymotrypsinogen were also detected but had low specific activities. Detailed two-dimensional analysis of the secretory protein composition of normal and neoplastic acinar cells is currently in progress.

Plans: We plan to isolate and characterize the composition of various subcellular fractions including exocrine proteins derived from the pancreatic acinar carcinoma and where possible compare with corresponding components of normal pancreatic acinar cells to detect qualitative and quantitative abnormalities of gene expression. Various subpopulations of pancreatic acinar carcinoma will be separated and their cytodifferentiation, tumorigenic potential and biochemical maturation will be established. We will also attempt to develop cell lines and the pancreatic acinar carcinoma into an ascites form for studies on modulation of differentiation.

Publications:

Reddy, J.K., Reddy, M.K., Hansen, L.J., Qureshi, S.A.: Secretion granules of transplantable pancreatic acinar carcinoma of rat. *Biochem. J.* 188: 921-924, 1980.

Reddy, J.K., Rao, M.S., Warren, J.R., Qureshi, S.A., Christensen, E.I.: Differentiation and DNA synthesis in pancreatic acinar carcinoma of rat. *Cancer Res.* 40:3443-3454, 1980.

Program Director: William E. Straile, Ph.D.

Hansen, L.J., Mangkornkanok/Mark M., Reddy, J.K.: Immunohistochemical localization of pancreatic exocrine enzymes in normal and neoplastic pancreatic acinar epithelium of rat. J. Histochem. Cytochem. 29:309-313, 1981.

Warren, J.R., Reddy, J.K.: Transplantable pancreatic acinar carcinoma. Cancer 47:1535-1542, 1981.

From 07/01/78 to 06/30/84

FY 81: \$51,500

Dr. Daniel M. Hays, Childrens Hospital of Los Angeles
4650 Sunset Boulevard, Los Angeles, California 90054

Objectives: The aim of this program is to disseminate information on the early detection and management of childhood cancer to medical, dental, nursing, and paramedical student groups, employing the faculty and facilities of a university-based Pediatric Oncology Center. These include: (a) specific curriculum alterations for medical students, (b) multidisciplinary teaching clinics developed for interns and residents in pediatrics, pathology, radiology, surgery, and the psychiatry-psychology fields; and post-doctoral trainees in oncology and related fields, and (c) educational projects initiated for social workers, oncology and pediatric nurses, paramedical personnel in the areas of radiotherapy, physiotherapy, rehabilitation, and activity programs, primary care physicians, and physician specialties in pediatric oncology-hematology, radiotherapy, or related disciplines throughout Southern California.

Accomplishments: These include (1) Medical School curriculum changes with major increase in time and a revision of the format for oncology training; (2) introduction of undergraduates into the active function of a large multidisciplinary oncology clinic; (3) evaluation of the learning experience of Year III medical students in pediatric oncology, employing serial questionnaires (250 students), with resulting changes in the objectives and methods; (4) Clinical Assistantships provided for 45 students from 20 medical schools, the major element of which was an individual oncology-related research project, directly supervised by faculty members; (5) the development of teaching programs in both Therapy and "Follow-up" Oncology Clinics, employing a multidisciplinary staff at a faculty level for students, Clinical Associates, practicing physicians in "refresher" status, and institutional residents and fellows; (6) Clinical Associates (23), supported for the purpose of (a) medical student, nurse, and house-staff teaching; (b) clinical research, associated with cooperative groups, and other studies; and (c) basic research in oncology; and (7) formation of educational programs for physicians (and others) interested in research or practice-oriented pediatric radiotherapy, surgery, or pathology with the aim of developing physicians capable of participating in multidisciplinary pediatric cancer management programs.

Plans: Emphasis will be on development of innovative programs for students (medical, nursing, etc.) and for generalists who require orientation in pediatric oncology. The revised medical school curriculum and its evaluation procedure is in its initial year, and will require modification. Expansion of the program for family practice trainees (Ventura County) and for general and pediatric practitioners (CHLA) is planned. The Clinical Assistant Program will be enlarged and reorganized to meet diverse student needs. Introduction of students in all cancer-related disciplines to the Cooperative Group concept, including aims and organizations, will be augmented. The Ocular Cancer Center will begin its ophthalmologist orientations. The Department

Program Director: Margaret H. Edwards, M.D.

of Pathology will complete the development of the Pediatric Tumor Center with its community-wide educational services. Expansion of the Cancer-Nutrition Project will include additional educational programs for physicians, nurses, and dietitians. Additional courses for nurses in pediatric oncology, relative to the Los Angeles "Home Care" Program are planned. Individuals with career goals in oncology, pediatric or oncologic surgery, radiotherapy, psychiatry, psychology, and pediatric or tumor pathology will be provided the opportunity for intensive orientation periods in this field.

From: 06/01/78 to 05/31/81

FY 81: -0- (Ann. \$62,832)

Dr. Daniel Dexter, Roger Williams General Hospital, Providence, RI 02908

Objectives: The objective of this project is to induce the differentiation of human colon carcinoma cells with chemicals such as the polar solvents dimethyl sulfoxide (DMSO) and N,N-dimethylformamide (DMF), and sodium butyrate. We hope to achieve an induction of differentiation markers, such as cell surface antigen and specific enzymes, as well as an alteration in the malignant phenotype of treated cultured cells. The inducing chemicals will also be used to treat human colon tumor xenograft growing in nude mice to determine whether these agents have an affect *in vivo*. Finally, we plan to combine inducing chemicals with conventional anticancer agents to see whether biological modifiers such as DMF can sensitize human colon cancer cells (both *in vitro* and *in vivo*) to chemotherapeutic drugs, ionizing radiation, heat, hormone therapy, or immunotherapy.

Accomplishments: Clone A cells, derived from the heterogeneous DLD-1 human colon cancer cell line, or DLD-2 cells (from a colon cancer cell line established from another patient's primary colon tumor) are injected subcutaneously and grown in nude mice. After tumors have reached a size of 5 mm by 5 mm, animals are randomized into two groups for each line. Group 1 receives 2000 mg/kg of DMF i.p. daily for 21 days, and Group 2 receives isotonic saline. In our most recent experiment, DMF treatment reduced HCT-15 and DLD-2 tumor growth by 65% and 67% respectively compared to saline-treated controls. These results confirm earlier data with these two colon carcinomas and suggest that the growth of some human colon cancer *in vivo* can be inhibited by DMF. Human colon cancer clone D or clone A cells (both clones isolated from the DLD-1 parent line) have been cultured in DMF-containing medium for 3-5 passages, and then x-irradiated. We irradiated cells not exposed to the polar solvent as a control. The irradiated cells are trypsinized from the culture dishes, resuspended, and plated into culture dishes with regular growth medium. When colonies that developed from the single cells reached a size of 50 or more cells, the cultures were stained, colonies counted, and survival curves generated. The data show that DMF sensitizes both clone A and clone D cells to ionizing radiation; the effect is most pronounced in the survival curves. This study indicates that chemical inducers of differentiation, such as DMF, can act as radiosensitizers, a finding that has clinical implication.

Plans: We will determine whether DMF sensitizes other cultured human colon cancer cells to x-irradiation, and whether other chemical inducers function as radiosensitizers. We will treat clone A and DLD-2 xenograft tumors with a combination of x-rays and DMF, versus DMF or ionizing radiation alone to see whether the polar solvent sensitizes colon cancer xenografts to x-irradiation.

Publications:

Dexter, D.S., Leith, J.T., Crabtree, G.W., Parks, R.E., Jr., Glicksman, A.S., and Calabresi, P.: N,N-dimethylformamide-induced Modulation of Responses of Tumor Cells to Conventional Anti-cancer Treatment Modalities. In Maturation Factors and Cancer, M.S.A. More, Ed. New York, Raven Press, in press.

Program Director: Vincent J. Cairoli, Ph.D.

Grant 23229: Clinical Cancer Education Program

From 7/1/77 to 6/30/82 FY 81: 96,472
Dr. Paul S. Engstrom, Fox Chase Cancer Center
7101 Burlholme Avenue, Philadelphia, Pennsylvania 19111

Objectives: This program is designed to continue the coordinated clinical cancer education program in the multi-disciplinary setting of the Fox Chase Cancer Center by educating students in medicine, dentistry, nursing and allied health professionals in the fundamentals of cancer diagnosis and management; providing practicing professionals engaged in general health care in the community with the fundamental knowledge and experience which will enable them to deliver improved care to cancer patients; training and educating professionals in oncology specialty disciplines; and evaluating the continuing education program for community professionals.

- Accomplishments: 1. Four preclinical medical students participated in the clinical assistant rotations at the American Oncologic Hospital where the emphasis was on history taking, physical examination skills and observation of multi-disciplinary cancer management.
2. Forty-two medical or osteopathic medical students participated in elective clerkships in oncology. Sixteen interns and residents in surgery elected the surgical oncology residence at the Fox Chase Cancer Center.
3. Five medical fellow trainees received training at the Fox Chase Cancer Center in the Clinical Associate Program in Medical Oncology. Two gastroenterology residents completed three month electives in oncologic gastroenterology.
4. One hundred and twenty-six diploma or associate degree nursing students rotated to the American Oncologic Hospital for the multi-disciplinary cancer patient care course. One graduate student and five pediatric nurse practitioner students elected clinical experience at the center. Numerous nursing students from area schools of nursing were exposed to one-day cancer nursing care rotations.
5. Two social worker trainees received three month experience in psychosocial support of cancer patients and a Delaware Valley Social Worker Oncology Group was established to provide seminar experience for 100 professionals in two open meetings.
6. Three residents in rehabilitation medicine rotated to the hospital for experience in patient consultation and techniques of clinical physiologic testing of cancer patients.
7. Seventeen medical and osteopathic physician practitioners and 79 dental practitioners completed the re-education course in office diagnosis and management of cancer. In addition to the numerous trainees mentioned that received specific training, a series of seminars for practicing physicians was conducted, and weekly research conferences and clinical conferences in cancer were conducted for area health professionals.

Program Director: Margaret H. Edwards, M.D.

Plans: The Cancer Education Program of the Fox Chase Cancer Center will continue to emphasize outreach education to community health professionals as well as specialized training programs for medical students, residents, nursing students, oncology specialists and post-graduate trainees.

From 06/30/77 to 11/30/82 FY 81: \$753,251
Dr. Paul Engstrom, Fox Chase Cancer Center, 7701 Burholme Avenue
Philadelphia, Pennsylvania 19111

Objectives: The goal is the systematic application of validated technology differentially focused on selected lay and professional populations to achieve reduced cancer disability and mortality through a network of community health care facilities. Objectives: (1) identification of potential methods developed in research settings; (2) testing of these techniques in community settings; (3) evaluation of their applicability for widespread community use; and (4) the elevation of cancer control from a string of activities to a comprehensive multidisciplinary program.

Accomplishments: We continue: (1) a hospital Needs Assessment Survey in a six-county area of Pennsylvania and Southern New Jersey; (2) the development and implementation of model training programs for dentists and family practitioners; (3) provision of clergy training for pastoral counselors; (4) the development of valid measures of patient physical function for use as clinical instruments and research tools; (5) sponsorship of the Mid-Atlantic Social Work Oncology Group Newsletter, conferences and training courses; (6) outreach education and training for nurses and allied health professionals; (7) development and dissemination of site-specific management guidelines; (8) epidemiologic studies of cancer counseling; (10) patient oriented colorectal management guidelines; (12) an assessment of cancer nursing training needs; (13) evaluation of our dental courses; (14) an assessment of all head and neck referrals; (15) a two-week course in tumor registry administration; (16) a data management seminar for hospital administrators and physicians.

Plans: (1) Continue and expand hospital and tumor registry surveys in Pennsylvania; (2) explore and test consortium strategies in two to three targeted areas; (3) develop cancer data collection system for targeted areas; (4) continue outreach education for health professionals; (5) research in area of nutritional supports; (6) development of home care hospice program; (7) develop patient education methods and materials; (8) implement a study of adolescent smoking; (9) develop a patient and family support group and (10) an investigation of risk factors in cancer etiology.

Publications:

Engstrom, P.F., for the Breast Cancer Task Force, Philadelphia Division, American Cancer Society: Pretreatment Evaluation of the Patient with Suspected or Proven Breast Cancer. Philadelphia 75:208-211, 1979.

Engstrom, P.F.: Cancer Patient Management. Curr. Concepts Oncol. 1(4): 2-3, 1979.

Dayal, H.: On Obtaining Size Measures for Population Surveys in Developing Nations - A Case Study. American Statistical Association, Proc. of the Social Statistics Section, pp. 303-3-5, 1979.

Program Director: Carlos E. Caban, Ph.D.

- Moolgavkar, S., Venzon, D.: A Two-Event Model for Carcinogenesis: Incidence Curves for Childhood and Adult Tumors. *Math. Biosci.* 47:55-77, 1979.
- Paul, A.R., Engstrom, P.F.: Diagnosis and Management of Cancer of the Pancreas. *Clinical Cancer Briefs*, Vol. 1, No. 5, May, 1980.
- Moolgavkar, S.H., Day, N.E., Stevens, R.G.: Two-stage Model for Carcinogenesis: Epidemiology of Breast Cancer in Females. *J. Nat'l. Cancer Inst.* 65:559-569, 1980.
- Ferguson, J., Rogers, J.D. (eds). *Topics in Clinical Nursing, Oncology Issue*, Vol. 2, No. 4, January, 1981.
- Epting, S.P.: Coping with Stress Through Peer Support. *Topics in Clinical Nursing Oncology Issue*, Vol. 2, No. 4, January, 1981.
- Moolgavkar, S.H.: The Neyman-Scott Carcinogenesis Model for Low-Dosage Extrapolation. *Math. Biosci.* 50:115-156, 1980.
- Bahn, A.K., Grover, P.L., and Miller, D.G.: Decision Making in Cancer Screening by Risk Factor Analysis. In *Cancer Control: Contemporary Views on Screening, Diagnosis and Therapy*, Kessler, Irving (ed.). University Park Press, Baltimore, Md., 1980.
- Kirs, P.J., Herman, R.M.: Neuromotor and Neuropsychological Manifestations of "Total Therapy" in Children with Acute Lymphoblastic Leukemia. *Cancer Treat. Rev.*, pp. 1-10, 1980.
- Dayal, H.: Additive Excess Risk Model for Epidemiologic Interaction in Retrospective Studies. *J. Chronic Dis.*, Vol. 33:653-660-, 1980.

From 06/01/78 to 05/31/84

FY 81: est. \$42,552

Martin H. Goldrosen, M.D., Department of Surgical Oncology, Roswell Park
Memorial Institute, Buffalo, New York 14263

Objectives: Carcinoma of the pancreas is the fifth most lethal cancer in humans and its incidence is increasing. The almost uniform mortality associated with this disease is primarily related to the difficulty of establishing a diagnosis early in the course of the disease. For the past three years, we have explored the possibility that a microplate leukocyte adherence inhibition assay (LAI) might be useful in identifying patients with pancreatic cancer and discriminate them from patients with other types of malignant disease or patients with benign disease whose symptom complex is similar to pancreatic cancer. The principle of the LAI assay is that leukocytes from a sensitized host become less adherent to a glass surface in the presence of a tumor extract to which the host is sensitized. The development of the microplate LAI assay into a diagnostic test for pancreatic cancer may result in earlier detection and ultimately improve survival for pancreatic cancer patients.

Accomplishments: To date, 228 individuals have been evaluated by the microplate LAI assay on one or more occasions. Of these 228 individuals, 67 had histologically confirmed pancreatic adenocarcinoma. Overall, 69 percent of these patients were sensitized only to a pancreatic organ specific neoantigen and no other neoantigen. When this data was further subdivided on the basis of surgical staging, the following patterns of sensitization became apparent. Eighty-eight percent of patients with localized disease (no nodal involvement) and 72 percent of patients with regional disease (nodal involvement) were sensitized to a pancreatic organ specific neoantigen. However, after the tumor has metastasized to secondary organs, the degree of sensitization depended upon the site of the metastatic disease. Eighty-six percent of pancreatic cancer patients with extra-hepatic, 67 percent of pancreatic cancer patients with hepatic and extra-hepatic and 37 percent vs patients with hepatic metastasis displayed sensitization to an organ specific neoantigen. In contrast, less than five percent of the controls (other malignant benign disease and normals) display the same pattern of sensitization to a pancreatic organ specific neoantigen. Thus, the microplate LAI assay can detect a tumor specific immune response to a pancreatic organ specific neoantigen. This response was generally present when the pancreatic malignancy was relatively localized. However, as the primary tumor grew and metastasized to the liver fewer patients reacted. The effect of two chemotherapeutic agents (5-fluorouracil (FU) and adriamycin) on the LAI response was also evaluated. Of the patients receiving 5FU, 17 displayed sensitization to a pancreatic organ specific neoantigen before therapy. Following therapy, 13/17 still displayed the same pattern of sensitization in the LAI assay. Of the patients receiving adriamycin, 16 displayed sensitization to a pancreatic organ specific neoantigen before chemotherapy. Following therapy, only 5/16 still displayed the same pattern of sensitization in the LAI assay. Thus, 5FU had no major effect on the pancreatic cancer patient's ability to generate a specific anti-tumor response, whereas adriamycin abrogates the patient's ability to generate a specific anti-tumor response.

Program Director: William E. Straile, Ph.D.

Plans: To further increase the diagnostic potential of the microplate LAI assay, we plan to study why pancreatic cancer patients with more advanced disease are generally non-reactive. These studies will define the specific role of mononuclear cells in the microplate LAI assay as well as determine if pharmacological mediators can restore specific immune reactivity to non-reactive mononuclear cells.

Publications:

Goldrosen, M.H., Dasmahapatra, K., Jenkins, D., Howell, J.H., Arbuck, S.G., Moore, M.C. and Douglass, H.O., Jr.: Microplate Leucocyte Adherence Inhibition (LAI) Assay in Pancreatic Cancer: Detection of Specific Antitumor Immunity with Patients' Peripheral Blood Cells and Serum. Cancer, 47:1614-1619, 1981.

Grant 23653: Prolactin Binding in Normal and Neoplastic Prostate

From 08/01/78 to 07/31/81

FY 81: \$83,579

Dr. Raphael J. Witorsch, Department of Physiology, Medical College of Virginia,
Virginia Commonwealth University, Richmond, Virginia 23298

Objectives: The goal of this research is to elucidate the physiology of prolactin in normal and abnormal prostate. Our grant from the National Prostatic Cancer Project has enabled us to continue our development of an immunohistochemical assay for the visualization of prolactin binding sites in normal and abnormal rat prostate tissue, an approach which will prove useful both for research and diagnostic purposes. We have made significant refinements in the method in terms of sensitivity, specificity and quantitation and have applied this methodology to human prostate specimens. Using our approach we have demonstrated significant differences in the distribution of prostate prolactin binding sites and its testicular dependence among the ventral lateral and dorsal lobes of rat prostate which provides evidence for geographic variations in the endocrine control of prostatic function. We are also using immunohistochemistry to determine whether the extent of prolactin binding activity is associated in a positive or negative sense with the growth rate of R3327 rat prostatic cancers. We have also discovered by immunohistochemistry human placental lactogen immunoreactivity in growth hormone cells of rat pituitary gland. This finding suggests the existence of a new pituitary hormone which possesses both lactogenic and somatotrophic effects and may have prostatotrophic actions. Recently, we discovered that rat prostate tissue rapidly alters the immunoactivity of prolactin, a finding which may have bearing on the role and mechanism of action of this hormone.

Accomplishments: As a result of implementing modifications in our immunohistochemical method we have significantly enhanced its sensitivity. We can now detect prolactin binding sites in rat ventral prostate epithelial cells after incubating tissue sections with hormone concentrations as low as 6.25 ng/ml which is well within the physiological range. We have also demonstrated that prolactin binding is saturable in rat prostate and specific for hormones with lactogenic biological activity. Similar experiments using human prostate tissue specimens have resulted in significant enhancement of this assay and have provided evidence for the saturability and specificity of the prolactin binding site in human prostate tissue. Recently, we found that an electrophoresis densitometer can be used to obtain absorbance information from immunostained tissue. With the densitometer we can now quantitate prolactin binding in individual cells, and objectively compare different tissue specimens which indicates the utility of this instrumentation toward quantitating our method. We have initiated experiments which will lead to the localization of the prostatic binding site at the ultrastructural level. Pituitary tissue has been embedded in araldite and we are currently attempting to define conditions necessary for the penetration of immunoreagents into this tissue section. We have shown that homogenates of rat ventral prostate produce a time and dose dependent loss in prolactin immunoreactivity which greatly exceeds the capacity of the tissue to specifically bind the hormone. This prolactin altering activity predominates in the mitochondrial fraction and is enhanced at acid pH. Inhibitor analyses reveals that prolactin altering activity is inhibited by thiol group protease inhibitors but not by cathepsin antagonists,

Program Director: Andrew Chiarodo, Ph.D.

metallo group inhibitors or serine group protease inhibitors. We are currently trying to identify and elucidate endocrine factors controlling this activity.

Plans: We plan to extend our studies to define the physiological role of prolactin in normal and abnormal prostate and to discern whether this prolactin altering activity which we have discovered is involved in prostatrophic effects. We also plan to further develop immunohistochemistry as a quantitative and diagnostic tool at both the light and untrastructural levels. Finally, we hope to determine whether human placental lactogen in rat pituitary gland is a new hormone possessing prostatotrophic effects.

Publications:

Article published in a book:

Witorsch, R.J.: Visualization of Prolactin Binding Sites in Prostate Tissue. In Murphy, G.P., Sandberg, A.A. and Karr, J.P. (Eds). The Prostatic Cell, New York. Alan R. Liss, Inc. 1981. (In Press).

Grant 23665: Hormone and Radiation Therapy of Prostatic Tumors

From 09/30/78 to 08/31/81

FY 81: \$0 (Ann. \$125,751)

Dr. W.D.W. Heston, Division of Urology, Department of Surgery, Washington University, 4960 Audubon, St. Louis, Missouri 63110

Objectives: The objectives of the proposed research are as follows:

- (1) To determine the responsiveness of the rodent prostatic tumor lines to hormonal and radiation therapy.
- (2) To characterize the metastasis following hormonal and radiation therapy and to establish a stable transplantable metastatic tumor cell line.
- (3) To correlate the response of the tumor therapy with the various steroid receptors before, during, and after treatment.
- (4) To investigate the usefulness of prostate specific acid phosphatase and sialyltransferase as a means of identifying metastases and assessing tumor burden.
- (5) To develop an in vitro clonogenic assay to measure the tumor's response to in vivo and in vitro treatments.

Accomplishments: We have established the hormonal responsiveness to the various prostatic lines. The nonmetastatic anaplastic tumor has been characterized both in vivo and in vitro for radiation responsiveness.

We have established a metastatic anaplastic variant from the nonmetastatic anaplastic R5323AT line. We are still attempting to derive a metastatic variant from the more differentiated lines (R3327, R3327HI, R3327HF).

In this year, we are correlating the behavior of the metastatic R3327MAT-Lu and nonmetastatic R3327AT for biologic behavior and protease and sialyltransferase activity. Prostatic acid phosphatase studies will not be initiated until a metastatic tumor is developed which produces the prostatic fraction of acid phosphatase. The 3327MAT-Lu does not produce prostatic acid phosphatase.

Clonogenic assays for the R3327AT Tumor have been developed. Current investigations are in progress to develop clonogenic assays for the R3327H, HI, and HF variants.

Plans: Once we establish which biochemical parameters are important for the metastatic process of this tumor, we hope to use that information to predict the malignant potential of prostatic adenocarcinomas, and to use that information to develop methodologies to prevent the development of metastases or to select against those metastases once they have occurred.

Program Director: Andrew Chiarodo, Ph.D.

Publications:

Heston, W.D.W. and Lazan, D.W.: High Dose Estrogen Response of the Hormone Independent R3327-AT Copenhagen Rat Prostatic Tumor. Cancer Lett. 11:57. 1980. (Amsterdam.)

Heston, W.D.W., Kadmon, D., and Fair, W.R.: Effect of High Dose Diethylstilbestrol and ICRF-159 on the Growth and Metastases of the R3327 MAT-LyLu Prostatic Derived Tumor. Cancer Lett., (In Press).

Heston, W.D.W., Lazan, D.W., and Fair, W.R.L Aminoquanidine Reversal of the Inhibitory Effects of Ornithine Analogs on the Clonogenic Survival of the R3327-AT Prostate Derived Tumor. Cancer Lett., 11:323. 1981. (Amsterdam).

Kadmon, D., Heston, W.D.W., and Fair, W.R.: Effect of Surgery and Adjuvant Chemotherapy on the R3327 MAT-LyLu Tumor. Prostate, (In Press).

Lazan, D.W., Heston, W.D.W., and Fair, W. R.: Diethylstilbestrol Inhibition of Metastases by the R3327 MAT-Lu Copenhagen Rat Prostatic Tumor. Cancer Res. Submitted.

Heston, W.D.W., Kadmon, D., and Fair, W.R.: Growth Inhibition of a Prostatic Tumor by Difluoromethylornithine (DFMO) and by Cyclophosphamide. Int. J. Cancer. Submitted.

Rao, B.R., and Percz, C.A.: The Irradiation Response of Copenhagen Rat Prostatic Cancer. I. Poorly Differentiated Anaplastic R3327-AT Tumor. Int. J. Rad. Biol. & Phys. Submitted.

Rao, B.R., Fry, C.G., Kuhnel, R., Hunt, S., Dandliker, W.B.: A Fluorescent Probe for Rapid Detection of Estrogen Receptors. Cancer, 46:2902. 1980.

From 07/01/78 to 06/30/81

FY 81: \$0 (Ann. \$114,888)

Dr. Herbert H. Wotiz, Departments of Biochemistry and Urology, Boston University School of Medicine, 80 E. Concord Street, Boston, Massachusetts 02118

Objectives: Attempts to develop an assay for androgen receptors in prostate cancer tissue as possible indicators of appropriate therapy have been unsuccessful because of several problems. Among these were (1) the rapid metabolism of the natural steroid DHT even at low temperature (2) the presence of saturating amounts of endogenous hormone; (3) the relative instability of the receptor; and (4) the potential contamination of the tissue with SHBG which binds DHT with high affinity. While problems of DHT metabolism and SHBG contamination have been effectively dealt with by Raynaud's work on the development of synthetic androgens (R1881), we have concentrated on the questions of stability and quantitative exchange of endogenous ligand from cytosol and nuclei.

Accomplishments: Comparison was made of specific binding of ³HR-1881 to rat prostate cytosol between DCC adsorption and HAP precipitation procedures. Considerably better results were obtained with HAP, since DCC adsorption showed lower specific binding while non-specific binding was nearly three times as large. Another aspect relates to the temperature at which we exchange assay should be carried out. In a number of studies such exchange reactions were carried out at 15°C. We have found, however, that this leads to rapid receptor loss and accrual of high non-specific binding. Thus, overnight 0°C incubations have been shown to be more reliable. Since stability is a critical issue because of the long term, low temperature incubation, use of molybdate as a stabilizing agent was also investigated. The presence of 10mM molybdate clearly enhanced stability allowing recovery of nearly 30-50% more R1881 receptor sites. Evidence for retention of structural integrity in the presence of molybdate ion was obtained from sucrose density gradients (SDG) and equilibrium binding constants. Having resolved the problem of receptor stability, we next investigated better procedures for ligand exchange in cytosol and nuclei, since in vivo most of the prostate receptor sites are filled and translocated to the nucleus. As stated before, the exchange assay has to be carried out to 0°C due to receptor instability; however, because of the slow dissociation of DHT from the receptor, even after long time periods (16-24 h.) only a portion of the binding sites are exchanged with radioactive ligand. To accelerate DHT dissociation from the receptor we have utilized mersalyl acid (MA), a reagent previously shown to be effective for progesterone and vitamin D receptor dissociation. At concentrations of 0.2 mM, 95% dissociation of cytosol receptor from ³HR-1881 was achieved in 1 hr at 0°C. This loss of labelled ligand was verified by SDG. To be useful, this dissociation had to be reversible. 25mM monothioglycerol or dithiothreitol readily restored the binding activity (95%) in 2 h at 0°. This treatment did not affect the integrity of the receptor since the equilibrium binding constants and sedimentation values were equal to those of native receptor. Similarly, incubation of nuclei with 0.2mM mersalylacid at 0° for 30 min induced dissociation of androgen receptor complexes; this effect is reversible by addition of thiol reagents. Furthermore, addition of hydroxylapatite to the nuclei induced receptor recovery by preventing losses into the wash medium after exchange.

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Plans: Similar methodology has been applied to human prostatic tissue specimens from radical and transurethral prostatectomies, preliminary experiments suggest that the use of this reagent improved the exchange assay at low temperature. Further work has to be done to optimize this assay in human tissue. Estrogen receptor will also be quantitated in these same specimens. When sufficient data are available, clinical correlations will be made on patients treated with some form of hormonal addition or ablative therapy with the levels and ratios of cytosolic and nuclear androgen receptors and estrogen receptors.

Publications:

Traish, A.M., Muller, R.E., Burns, E.M., and Wotiz, H.H., Steroid Binding Proteins in Rat and Human Prostate; in The Prostatic Cell: Structure and Function. Pergamon Press, New York, 1981.

Grant 23699: Characterization of Cells Grown from Human Prostate

From 08/01/78 to 07/31/81

FY 81: \$0 (Ann. \$95,330)

Dr. Donald J. Merchant, Department of Microbiology, Eastern Virginia Medical School, P.O. Box 1980, Norfolk, Virginia 23501

Objectives: Two major objectives were set for this program.

1. Definition of conditions for primary culture of human prostate tissue leading to a system capable of use in prognosis and/or in vitro evaluation of chemotherapeutic modalities for individual patients.
2. Characterization of biochemical/genetic markers specific for prostatic acinar epithelial cells grown in culture (either primary or as established lines).

Accomplishments: We have completed the characterization of a primary culture system (see Pub. #1 below). In addition, studies are well under way to adapt this model to the evaluation of chemotherapeutic agents on cells of individual patients. Using Cisplatin we have obtained good dose response curves in the therapeutic range. Indicators of drug action investigated have included morphological changes, aberrations in RNA and DNA as shown by May-Grunwald-Giemsa staining, mitotic inhibition and changes in folic acid uptake. Biochemical/genetic markers are being separated from prostatic fluid and from acinar cells (BPH) by gel electrophoresis and isoelectric focusing and by solubilization and extraction respectively. Antiserum against prostatic fluid components has been prepared by hyperimmunization of mice. One antiserum appears to be specific for acinar cells when tested on frozen sections of prostate tissue by indirect immunofluorescence. Antibodies prepared against a combination of BPH extract and prostatic fluid in a mouse hybridoma system, when tested by indirect immunofluorescence specifically stain the perinuclear (golgi) area of the cells. Extensive studies of the primary culture system using phase contrast, scanning and transmission electron microscopy, time-lapse cinematography, histochemical staining and other approaches have enabled us to characterize the initial events in primary culture and to describe the phenomenon of dysplastic change as well as to partially characterize it.

Plans: The funding for this project expires on 07/31/81. With requested continuation support we hope to perfect the in vitro chemotherapy testing system and evaluate its usefulness in predicting effectiveness of agents in specific hosts as well as to assess its usefulness for prognosis. We also hope to further characterize a number of markers for acinar or basal cells and to demonstrate their usefulness in cell culture studies. Finally we hope to further characterize primary prostate cultures and to elucidate the nature and significance of dysplastic change.

Publications:

Clarke, S.M., and Merchant, D.J.: Primary Cultures of Human Prostatic Epithelial Cells from Transurethral Resection Specimens. The Prostate 1:87-94, 1980

Program Director: Andrew Chiarodo, Ph.D.

Merchant, D.J.: Virology Studies and Cell Lines for Prostate Cancer. The Prostate 1:215-225, 1980.

Papers Presented:

Clarke, S.M., Starling, J.J. and Merchant.: Hybridoma Antibodies Against Human Prostatic Tissue Antigens. Annual Meeting, Southeastern Cancer Research Assoc. Atlanta, November 1980.

Merchant, D.J. and Clarke, S.M.: In Vitro Development of Human Prostate Epithelium. International Symposium on Normal and Abnormal Growth and Differentiation Cancer Research Institute, Bombay, India, November 1980.

Clarke, S.M., Starling, J.J. and Merchant, D.J.: Hybridoma Antibodies Against Human Prostatic Tissue Antigens. First Annual Virginia Seminar of Cancer Research. Norfolk, March 1981 (Updated from the October paper).

Merchant, D.J. and Clarke, S.M.: Dysplastic Changes in Primary Cultures of Human Prostate Epithelium. First Annual Virginia Seminar of Cancer Research, Norfolk, March 1981.

Merchant, D.J. and Clarke, S.M.: Analysis of Primary Outgrowth from the Human Prostate Tissue Culture Association, Washington, D.C., June 1981.

Grant 23751: Cancer Rehabilitation Program -- Segmental Bone and Joint Replacement

From 01/01/80 to 12/31/81

FY 81: \$191,344

Dr. E. Y. Chao, Mayo Foundation, 200 First Street, S.W.,
Rochester, Minnesota 55905

Objectives: (1) to develop a prosthetic system for the replacement of bone after tumor resection, (2) to incorporate porous material in prosthesis design to improve implant fixation without bone cement, (3) to quantitate patients' joint functional changes after resections and prosthetic replacement, and (4) to establish better therapeutic and rehabilitation programs for functional improvement and implant protection. In cancer amputees, effective gait training methods will be developed. Booklets to describe the surgery, prosthesis, and special postoperative care will be prepared as patient education material. Workshops will be organized to disseminate knowledge gained and techniques developed to other cancer centers and physicians involved in the treatment of patients with resectable bone and soft tissue tumors.

Accomplishments: To date, a total of 156 patients have received custom segmental bone and joint prostheses. Among these patients, 107 have had bone and soft tissue tumors. Twenty-three percent had metastatic lesions and the remaining involved only primary lesions. The survival rate in the primary group involving the proximal femur is 78% after a mean period of 64 months of follow-up. In the metastatic group, 50% of the patients are still alive after an averaged follow-up period of 20 months. Cemented custom prostheses for the hip, knee and shoulder joints have been standardized with incremental segment lengths. Porous fiber-metal segmental bone prosthesis has been developed for clinical trial. A new custom knee prosthesis with an improved hinge design allowing better joint motion without metal-to-metal contact has been designed. The proximal femur and humerus prostheses are being modified with interchangeable modular units. Fiber-metal coating has been added to the proximal femur prosthesis. These new implants are being evaluated using theoretical and experimental stress analysis techniques. Gait analysis and functional evaluation are performed on every patient coming back for follow-up examination. Their results are summarized and graphed by a computer to report to the physicians. In general, the patients, after custom hip and knee prosthesis replacement for primary tumors, have near-normal functional results. Proximal humerus replacement patients have limited function in the shoulder but the use of the forearm and hand has been quite satisfactory. Fifty-one AK amputees have been evaluated to identify their gait defects. Consistently better results were found in the group using the biofeedback device as a training aid. The first workshop on the design and application of tumor prostheses has been organized to meet here in October this year. A booklet for the patients with custom hip prostheses is published and available for limited distribution.

Plans: Newly developed implant components will be thoroughly tested.

Optimal geometry of the stem will be determined from the cross-sectional data collected from bone specimens. Fiber metal proximal femur prosthesis will be studied in dogs before its clinical trial. Patient functional evaluation and amputee gait training will be continued with improved instruments and data analysis techniques. Our experience will be presented and discussed at the forthcoming workshop to benefit other investigators and practicing physicians.

Program Director: Lawrence D. Burke

Publications:

Sim, F.H., Chao, E.Y., Pritchard, D.J., Salzer, M.: Replacement of the Proximal Humerus with a Ceramic Prosthesis: A Preliminary Report. Clin. Orthop. & Rel. Res., 146-161-174, 1980.

Chao, E.Y., Laughman, R.K., Tanaka, M., Sim, F.H.: Functional Gait Analysis of Tumor Patients following Custom Total Joint and Segmental Replacement Arthroplasty. Proc. of Int. Conf. on Rehabilitation Engineering, pp. 79-82, Toronto, 1980.

Askew, L.J., Chao, E.Y., An, K.N., Cooney, W.P., Morrey, B.F.: Functional Evaluation in Upper Extremity Total Joint Replacement Patients. Proc. of Int. Conf. on Rehabilitation Engineering, pp. 75-78, Toronto, 1980.

Chao, E.Y.: Mechanics of Bioceramic Endoprosthesis Using Conical Cone Fixation without Bone Cement. Advances in Bioengineering. Edited by Van C, Mow. pp. 89-92, ASME, New York, 1980

Chao, .E.Y., Sim, F.H., Pritchard, D.J., Shives, T.T., May, C.H.: Custom Designed Proximal Femur and Total Hip Replacement Booklet for Bone Tumor Patient Education. A Mayo Clinic Publication, 24 pages, October 1980.

Laughman, R.K., Bogard, S.D., Chao, E.Y., McPhee, M.C.: A New Approach to Amputee Gait Training. Proc. of 27th Annual ORS Meeting, P. 220, Las Vegas, February 1981.

Huiskes, R., Crippen, T.E., Bechtold, J.E., Chao, E.Y.: Analytic Guidelines for Optimal Stem Designs of Custom-made Joint Prostheses. (IN PRESS)

Sim, F.H., Chao, E.Y.: Hip Salvage by Proximal Femoral Replacement. (IN PRESS)

Grant 23789: Inhibition of Urinary Bladder Carcinogenesis by 2-Hydroxyethylretinamide

From 06/01/79 to 05/30/82

FY 81: \$123,274

Dr. R. Squire, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Objectives: The inhibition of urinary bladder carcinogenesis by 2-hydroxyethylretinamide (HER) is being investigated in rats exposed to N-Butyl-N-(4 Hydroxybutyl) nitrosamine (BBN). A study of the chronic toxicity potential of HER is also being conducted. It is our objective to further evaluate the preliminary evidence that non-toxic doses of synthetic retinoids can inhibit experimental bladder carcinogenesis. Prior studies have not included the full biological course of carcinogenesis or completely assessed the toxicological potential of retinoids.

Accomplishments: Three groups of 85 female Fisher 344 rats were administered 600 mg BBN by gavage over a 6 week period. Groups received HER in the diet (L5 u.M/kg) either before and during or starting immediately after BBN administration and throughout life. A control group received only HER solvents in the diet. Interim sacrifices were performed and remaining animals will be sacrificed at 24 months or when moribund. Macroscopic morphometric analyses of rat bladder mucosae from the 3 interim sacrifices showed a decrease in extent of tumor involvement after 1 year in rats receiving retinoid ($P \leq .01$). The decrease was most notable, i.e. 3-fold, in animals receiving HER only before and during carcinogen exposure, suggesting an effect on tumor initiation. Histopathological and electron microscopic evaluations are not yet completed.

Macromolecular synthesis studies on 15 rats sacrificed either at 6, 12 or 18 weeks following BBN exposure have shown no decrease of either DNA, RNA or protein synthesis in the urothelium of HER treated rats. There is an increase in all counts in animals receiving BBN versus control rats.

The toxicity studies consist of 3 groups of 25 female Fisher rats receiving different levels of HER in the diet for 24 months. The high dose group (5 uM/kg) was sacrificed at 12 months due to excessive morbidity and mortality as the result of vitamin A-like toxicity. It should be noted this is only 3.3 x the level in the tumor inhibition study. Overt toxicity is not yet apparent at lower exposure levels.

Plans: Remaining animals on the carcinogenesis and toxicity studies will be sacrificed, and histopathological and ultrastructural examinations will be completed during this final project year. We also plan to compare the results of transplantation of the bladder tumors into HER treated and control syngeneic recipients.

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Grant 23790: Cytochemical Probes of Urothelial Tumor Cells

From 09/01/78 to 08/31/81

FY 81: 0 (Ann. \$53,715)

M. Vanderlaan, Ph.D., Lawrence Livermore Laboratory, Livermore, California

Objectives: The objective of this study is to characterize early lesions by cytochemical methods in primary tumors. Using an animal model for studying early changes permits a controlled carcinogen exposure and an opportunity to interrelate histologic sections, urine cytology and the cytology of cells dissociated directly from the lesions. Such a controlled study on clinical material would be burdened by the technical difficulties associated with sample collection, preservation, and correlation with tumor pathology. The clinical application of the marker/probe combinations developed under this grant is an important aspect of the study.

Accomplishments: The project has had as its specific aim a pilot study to determine the feasibility of the rat bladder tumors as a model for cytochemical research. Emphasis has been placed on getting first hand experience with the lesions produced, their histology and ultrastructure, and on methods of cell collection, preparation and cytologic verifications of the model. In the area of the new cytochemical probes, it was initially thought that methodology developed in other areas of histochemistry could be readily applied to cytologic material. We have subsequently learned that a fair amount of method development is necessary, particularly in the area of validating the enzyme staining protocols. Thus, a second specific aim of the research year has been basic research in the area of enzyme cytochemistry.

Multiple evaluations of the same cell are being made to establish the connections between new cytochemical procedures, ultrastructural observations, and conventional cytology. Work in this area has just begun since the three modes of assessing cells were first developed independently.

Dissociated cells viewed in EM section show some changes induced by the dissociation process, although these are mostly reversible and are greatly reduced if the cells are allowed to recover before fixation. Dissociated cells stained by the Papanicolaou procedure may be identified and relocated in electron microscope sections.

Cyanophilia is a frequently observed feature of the cytoplasm of morphologically abnormal cells. Whether this increased density of cytoplasm correlates with the presence of the fiber bundles seen ultrastructurally remains to be determined. Multiple evaluations of the same cells should permit us to answer this question.

Cells stained on dialysis membranes may be restained using Papanicolaou stain. The membrane itself is sufficiently inert to withstand the various steps in Papanicolaou staining. There is loss of nuclear detail resulting from the air drying that occurs in cells processed on dialysis membrane however. Current efforts are being made to judge abnormal cell morphology based on the propidium iodide/fluorescamine counterstains used in conjunction with the enzyme stains, rather than resort to the tedious procedure of locating cells of a particular

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enzyme content, restaining them with Papanicolaou stain, and relocating them for cytopathologic evaluation.

Plans: The three views of the urothelium provided by new enzyme staining methods, Papanicolaou staining, and electron microscopy are being correlated in an effort to develop an integrated picture. The mutual compatability of the various methods is being explored with the objective of evaluating the same cell with two or more methodologies.

Grant 23800: Induction of Unscheduled DNA Synthesis in Primary Culture of Dog, Rat and Mouse Urothelial Cells by Arylhydroxylamines, N-Arylhydroxamic Acids and Nitroheterocycles

From 09/01/78 to 08/31/81

FY 81: \$0 (Ann. \$92,318)

Dr. C.Y. Wang, Michigan Cancer Foundation, Detroit, Michigan

Objectives: The primary objective of this study is to examine the ability of urothelial cells of various species to activate carcinogenic arylhydroxylamines, N-arylhydroxamic acids and nitroheterocycles.

Accomplishments: UDS, which has been used to detect the interaction between DNA and carcinogens, is used as a probe for the present study. 2-Aminofluorene (AF), 4-aminobiphenyl (ABP), 2-aminonaphthalene (AN) and their respective N-hydroxylamines (N-OH-AF, N-OH-ABP and N-OH-AN) and acetyl hydroxamic acids (N-OH-AAF, N-OH-AABP and N-OH-AAN), as well as 2-amino-4-(5-nitro-2-furyl)thiazole (ANFT) and 4-nitroquinoline 1-oxide (NQO) were incubated with primary cultures of urothelial cells from dogs, rats or mice for 1.5 hr. Washed cultures were then incubated with ³H-thymidine and N-hydroxyurea for 2 hr., and UDS was measured by autoradiography. Compounds which caused UDS were: NQO >> N-OH-AF = N-OH-AFF > N-OH-AN > ANFT in rat cells; NQO >> N-OH-AF = N-OH-ABP > N-OH-AN in mouse cells; and NQO >> N-OH-AFF > N-OH-ABP in dogs cells. The activity of N-OH-AAF but not of N-OH-AF in rat and dog cells was decreased 50% by 10 uM paraoxon.

Similar results were obtained when the cells were simultaneously treated with the carcinogens and ³H-thymidine for 16 hr. except that neither ANFT nor NQO induced UDS.

These compounds induce bladder tumors in dogs (AAF, ABP, AABP, AN and FANFT), rats (AAF, AN, and FANFT), and mice (AAF, ABP, and FANFT). Thus, there is a correlation between the bladder carcinogenicity of these compounds and the ability of their metabolites to induce UDS in urothelial cells, with the exception of AN and FANFT in dogs and FANFT in mice. The selective responsiveness of urothelial cells to certain metabolites in rat (N-OH-AF, N-OH-AAF), mouse (N-OH-AF), and dog (N-OH-AAF), suggests that urothelial cells from different species may have different activation mechanisms for arylamine metabolites. The data also suggest that urothelial cells may have nitroreductase for the activation of NQO and nitrofurans.

Plans: The urothelial enzymes which may be involved in the activation of these carcinogens will be identified in further experiments.

Publications:

Shirai, T.: Lack of Enhancing Effect of Mucosal Regeneration Following Ulceration of the Urinary Bladder on N-butyl-N-(4-hydroxybutyl)Nitrosamine Carcinogenesis in Rats. Cancer Res. 40: 3709-3712. 1980.

Shirai, T., and Wang, C.Y.: Enhancement of Sister-Chromatid Exchange in Chinese Hamster Ovary Cells by Nitrofurans. Mutation Res. 79: 345-350. 1980.

Program Director: William E. Straile, Ph.D.

Grant 23855: Suppressor Cell Activity in Bladder Cancer

From 07/01/78 to 06/30/81 FY 81: \$0 (Ann. \$80,648)
Dr. William J. Catalona, Department of Surgery/Urology, Washington
University School of Medicine at the Jewish Hospital of St. Louis,
Missouri

Objectives: The objectives of this proposal were to test blood (PBL) and lymph node (LNC) lymphocytes for: (1) spontaneous suppression of cell-mediated cytotoxicity (CMC) against 253J human bladder cancer cells, (2) concanavalin A-(Con A) induced suppressor cell activity, (3) suppression of cytotoxicity induced in a mixed lymphocyte-tumor cell interaction, and (4) spontaneous suppression of natural killer (NK) cell activity. Suppressor extracts prepared from ultrasonically disrupted PBL or LNC also were to be tested.

Accomplishments: Previously we had shown that NK activity is depressed in urologic cancer patients, and that the depression correlated inversely with heightened macrophage activity, suggesting a possible cellular regulatory mechanism. We also demonstrated the presence of Con A-inducible suppressor cell activity in PBL and LNC of urologic cancer patients and controls, but there was no difference between the two groups even though many of the cancer patients had impaired lymphocyte proliferative responses. We had also made the serendipitous discovery that protein A from Staphylococcus aureus is a potent inducer of type II interferon in human lymphocytes.

During the past year we demonstrated spontaneous suppression of NK in LNC of some bladder cancer patients and in extracts prepared from LNC. In a new series of experiments we have fractionated PBL and LNC into adherent cells, nonadherent cells, T cells, T_G cells and T-non-G cells. We have observed heightened proliferative responses in the nonadherent and T-non-G subpopulations and low responses in T_G cells. In cell mixing experiments, addition of adherent cells to nonadherent cells or of T_G cells to unfractionated cells resulted in significant suppression of the proliferative response. In contrast, addition of T-non-G cells to unfractionated cells enhanced the proliferative response. These results suggest that the T_G and adherent cell subpopulations may serve as useful probes to study spontaneous suppressor cell function in bladder cancer patients.

Plans: We will examine systematically the various types of spontaneous suppressor cells that have been operationally defined in humans in fractionated cell subpopulations including suppression mediated by T cells [(i) T_G, (ii) histamine-receptor bearing, and (iii) soybean agglutinin resistant suppressor cells] as well as those mediated by suppressor macrophages [(i) glass-adherent, (ii) prostaglandin-secreting, and (iii) "short-lived" adherent suppressor cells]. We will examine the development of suppressor cell activity in relation to tumor burden and how it can be modulated. We also will continue our studies of suppressor extracts, but will prepare them from fractionated cell subpopulations.

Program Director: William E. Straile, Ph.D.

Publications:

- Catalona, W.J., T.L. Ratliff and R.E. McCool. 1980. Con A-activated Suppressor Cell Activity in Peripheral Blood Lymphocytes of Urologic Cancer Patients. J. Natl. Cancer Inst. 65:553
- Catalona, W.J., T.L. Ratliff and R.E. McCool. 1980. Characterization of Interferon Induced in Human Lymphocytes by Staphylococcal Protein A. Surgical Forum XXXI:591.
- Ratliff, T.L., R.E. McCool and W.J. Catalona. 1981. Interferon Induction and Augmentation of Natural Killer Activity by Staphylococcus Protein A. Cell Immunol. 57:1.
- Catalona, W.J., T.L. Ratliff and R.E. McCool. 1981. Role of Antibody in Cytotoxicity by Lymphocytes Armed Against 253J Bladder Cancer Line. Int. Arch. Allergy and Appl. Immunol. (In Press).
- Catalona, W.J., T.L. Ratliff and R.E. McCool. 1981. Interferon Induced by S. aureus Protein A Augments Natural Killing and Antibody-dependent cmL. Nature (In Press).

Abstracts

- Ratliff, T.L., R.E. McCool and W.J. Catalona. 1980. Measurement of Concanavalin A-activated Suppressor Cell Activity in Normal and Tumor-Bearing Subjects. Abstract. Federation Proceedings 39:696.
- Ratliff, T.L., R.E. McCool and W. J. Catalona. 1980. Staphylococcus Protein A induces Interferon and Augments Natural Killer Cell Activity in Human Peripheral Blood Lymphocytes. Abstract. American Society for Microbiology.
- Catalona, W.J., T.L. Ratliff and R.E. McCool. 1980. Mitogen-induced Suppressor Cell Function in Peripheral Blood and Lymph Nodes of Urologic Cancer Patients. Abstract. American Urological Association, Inc.
- Ratliff, T.L., R.E. McCool and W.J. Catalona. 1981. Characterization of the Lymphocyte Subpopulation Producing Interferon Gamma after Stimulation by Protein A from Staphylococcus Aureus. Abstract. Federation Proceedings 40(3):1129.

Chapters in Books

- Catalona, W.J., T.L. Ratliff and R.E. McCool. 1980. Immunology of Genito-urinary Tumors. In Genitourinary Malignancy Vol. I (Editor, F. Paulson, M.D.) Plenum Press Publ. Co. (In Press).
- Catalona, W.J., and R.E. McCool. 1980. Immunotherapy of cancer. In Recent Advances in Urologic Cancer. (Editor, N. Javadpour) Williams and Wilkins Publ. Co. (In Press).

From: 09/30/78 to 08/31/84

FY 81: \$103,961 (est.)

Dr. Tracy D. Wilkins, Virginia Polytechnic Institute and State University, School of Agriculture and Life Sciences, Blacksburg, VA 24061

Objectives: An active mutagen has been isolated and purified from human feces. This mutagen is present in high levels in feces of a large enough number of North Americans to suggest a possible role in colon cancer. Our objectives are to structurally identify this compound, study its formation in our in vitro incubation system, and determine which organism(s) in the normal fecal flora may be responsible for its production.

Accomplishments: We have purified the mutagen by anaerobic high pressure liquid chromatography, obtained a presumptive molecular weight (651 daltons) and structure (polyene), characterized its oxygen lability and stabilized the compound in organic and aqueous solvents with antioxidants and strict reduced conditions respectively, developed an in vitro incubation system with which we can increase our yields as well as study the effects of nutritional supplements and metabolic inhibitors, shown that the mutagen is produced in the colon by fermentation of anaerobic microorganisms, and shown that bile and bile acids can significantly increase mutagen production in vitro.

Plans: Our future goals are: to determine the chemical structure of this fecal mutagen and initiate organic synthesis thereof, to determine why feces of some individuals do not produce the mutagen upon in vitro incubation of their feces (are inhibitors present or do they lack important precursors?), to isolate an organism(s) from our donors that can produce the mutagen, to develop a culture media in which mutagen can be produced by fecal "seeds" and/or pure cultures of anaerobes, and to determine the genetic toxicity of this purified mutagen in mammalian cell systems.

Publications:

Lederman, M., Van Tassell, R.L., West, S.E.H., Ehrich, M.F., and Wilkins, T.D.: In Vitro Production of Human Fecal Mutagens. *Mutation Res.*, 79:115-124, 1980.

Wilkins, T.D., Lederman, M.L., Van Tassell, R.L., Kingston, D.G.I., and Henion, J.: Characterization of a Mutagenic Bacterial Product in Human Feces. *Amer. J. Clin. Nutr.*, 33:2513-2520, 1980.

Ehrich, M.F., Aswell, J.E., and Wilkins, T.D.: Alteration of the Mutagenicity of Human Fecal Extracts by Hepatic Microsomal Enzymes. *J. Toxicol. Environ. Health*, 7:107-115, 1981.

Program Director: Vincent J. Cairolì, Ph.D.

From 07/01/78 to 06/30/83 FY 81: \$74,784
Dr. Alvin Mauer, St. Jude Children's Research Center
332 North Landerdale, Memphis, Tennessee 38101

Objective: The primary objective of this Clinical Cancer Education grant is to train clinicians who can assume care of cancer patients with expertise in diagnosis and management and who can utilize, in patient care, multiple subspecialty and basic research disciplines. Specifically, this grant supports the training of clinical assistants and clinical associates.

Accomplishments: The purpose of this program is to prepare the clinical associate for an academic career in pediatric hematology-oncology. The training goals include: (1) proficiency in the diagnosis and management of children with leukemia, solid tumors and blood disorders and (2) participation in cancer research. The two-year clinical training program requires that the clinical associate spend equal time each year on three services: (1) leukemia, (2) solid tumors and (3) hematology.

Clinical assistants are medical or dental students who are accepted during their summer periods or off-quarters to participate in cancer research traineeships at St. Jude Children's Research Hospital. Each student has his own sponsor who carefully supervises the students's performance. Each student is assigned to either a particular laboratory to conduct a cancer research project, or to one of the two cancer services, the leukemia service or the solid tumor service. In the latter case, the clinical assistant is trained in the diagnosis and management of childhood cancer as he works closely with the attending physician, clinical associates and pediatric residents.

The specific educational activity supported from 1980 through the current date has been the training of six clinical associates in the management and care of children with cancer. Three of these clinical associates were in their second year of post-residency training and three were in their first. In addition, eight clinical assistants have been supported for short-term cancer research traineeships in the following areas: hematology-oncology, virology, infectious diseases, immunology, pharmacology and biochemistry.

Plans: The training of clinicians and students as described above will be continued through support of this clinical cancer education program grant.

Program Director: Margaret H. Edwards, M.D.

From 12/01/80 to 11/30/83

FY 81: \$653,801

Dr. Joseph W. Cullen, UCLA Jonsson Comprehensive Cancer Center, 924 Westwood Blvd., Suite 940, Los Angeles, California 90024

Objectives: This grant provides operating support for the Division of Cancer Control, UCLA Jonsson Comprehensive Cancer Center, to: (1) provide administrative/management capabilities to carry out planning and evaluation functions for the development of outreach activities in this Center's service area (with particular emphasis in the complex and highly populated metropolis of Los Angeles); (2) interface all planning and program development with the vast resources available through the Cancer Center and its affiliated institutions; and (3) support programs now ready for community implementation and coordinate others now under development. While interest in and emphasis on all aspects of cancer control are included, particular emphasis is placed on cancer prevention, psychosocial rehabilitation, and professional and public education.

Accomplishments: From December 1, 1980 through November 30, 1981, the Division of Cancer Control staff planned, developed, and/or implemented several new programs among which are the following: (1) a graduated series of workshops addressing lung cancer prevention in the Los Angeles Basin, out of which eight component projects have been identified and planned; (2) the American Health Foundation's "Know Your Body" Program in the Los Angeles and Santa Monica Unified School Districts; (3) a Smoking Research and Prevention Center to coordinate existing, and encourage new, fundamental and applied smoking research, and also provide needed core support services related to this area of research; (4) a coordinated smoking research program project involving multidisciplinary approaches including biological, psychosocial/behavioral, and epidemiologic aspects of smoking; (5) professional education programs related to occupational carcinogenesis; (6) a project to study compliance patterns in patients treated with full course radiation therapy for tumors of head and neck region; (7) a public education program in cancer patient education through the Los Angeles County Public Library System; (8) the organization of a regional working group to plan and organize educational programs for nurses, social workers, and physical and occupational therapists; (9) a program designed to alleviate burnout and staff turnover in oncology wards at community hospitals through the establishment of collaborative teams; (10) a program to stimulate self-help group formation at local hospital/health information sites for cancer patients and/or their significant others; and (11) an epidemiological study of California physicians from 1950-1980 to determine their mortality trends from lung cancer and other causes of death as they related to decline in cigarette smoking over the past 30 years.

Plans: This report reflects the activities of the first year of a three-year renewal grant. Individual grant applications for certain of the above programs have also been submitted and are pending review and approval at this time. The remaining programs are active and will continue through the remaining portion of the above project period.

Program Director: Carlos E. Caban, Ph.D.

Grant 24079: Neuropsychological Effects of Leukemia and its Treatment

From 09/01/78 to 03/31/82 FY 81: \$136,372

Dr. Richard A. Berg, St. Jude Children's Research Hospital, 332 North Lauderdale,
Memphis, Tennessee 38101

Objectives: To determine long-term developmental effects of acute lymphoblastic leukemia (ALL) and its treatment, consisting of 2400 RAD's of CO₆₀ cranial irradiation and combination chemotherapy. The determinations are to be made by means of serial neuropsychological, electroencephalographic, and audiological evaluations.

Accomplishments: After a brief suspension, the project has been reinstated and is making excellent progress. Eighty-five patients between 5 and 12 years of age diagnosed as having ALL have received at least one complete evaluation since the beginning of this endeavor. Of these original 85 patients, we have identified and located 61 surviving patients (the remaining 24 having expired), all of whom have been scheduled for re-evaluation in the coming year. As preliminary evaluation of the computerized data base gathered in the early course of this study revealed much of the data to be incomplete with small parts of information unidentifiable, all original data has therefore been recomputerized to form a new and more complete data base to which new data will be entered as it is collected. Although it is still too early to positively identify the long-term neuropsychological effects of ALL and its treatment, preliminary analysis of the data gathered to date suggests that survivors score approximately 1 standard deviation below the general population mean on measures of psychometric intelligence. Additionally, a pattern suggestive of memory deficits and distractibility which may interfere with academic achievement appears to be emerging in these survivors. The initial data analyses obtained from the 85 patients receiving 2400 RAD's of cranial irradiation showed that 44.7% of the patients had had post radiation somnolence syndrome characterized by an order of decreasing frequency: lethargy, low-grade fever, nausea and vomiting. The implications of somnolence syndrome on future cerebral function can be delineated by comparing results of serial neurological examinations, cranial CT scan features and neuropsychological test performance of children with and without the syndrome.

Plans: Continued re-evaluation of the patients in the study and extensive analysis of the data gathered will enable the investigators to determine levels and patterns of neuropsychological performance among patients diagnosed as having ALL. We plan to develop an additional control group of non-patient children to allow for direct patient vs. non-patient comparisons of neuropsychological variables.

Publications:

Goff, J.R., Anderson, H.R., Jr., Cooper, P.F. Distractibility and memory deficits in long-term survivors of acute lymphoblastic leukemia. Dev. and Beh. Ped. 1 (4): 158-163, 1980.

Program Director: Lawrence D. Burke

Ch'ien, L.T., Aur, R.J.A., Verzosa, M.S., Coburn, T.P., Goff, J.R., Hustu, O., Price, R.A., Seifert, M.J., and Simone, J.V. Progression of methotrexate-induced leukoencephalopathy in children with leukemia. Medical and Pediatric Oncology, (IN PRESS)

Grant 24118: Gynecologic Cancer Education

From 12/01/78 to 11/30/81

FY 81: \$229,183

Dr. H. M. Shingleton, University of Alabama, Birmingham, Alabama 35233

Objectives: Nurse Practitioner Program: To prepare nurse practitioners to provide cancer detection and other health services to women in health manpower shortage areas and to upgrade skills of previously trained clinicians.

Trophoblastic Disease: To provide education to practicing physicians in a five-state area and assistance in managing women with gestational trophoblastic neoplasms.

Colposcopy Program: To train physicians in colposcopy and to provide educational materials for patients and physicians in regional clinics.

Accomplishments: The accomplishments for the current year include: (1) Seventh Annual Scientific Session for Nurse Practitioners, April, 1981 (85 participants), (2) A publication, "The Role and Practice of Ob-Gyn Nurse Practitioners in Health Departments and Private Practice Settings," submitted to Nurse Practitioner, (3) Accreditation by the Central Regional Accrediting Committee of the American Nurse Association for the Nurse Practitioner Program, and (4) an increase in referrals for assistance with trophoblastic disease patients with over 1,000 HCG titers and physician contacts occurring during the year. Twelve patients have been hospitalized for chemotherapeutic treatment of high risk disease as a part of this program.

Plans: Nurse Practitioner Program: This program will be funded through other sources in conjunction with the School of Nursing of the University of Alabama in Birmingham, offering both Master's level academic credit and continuing education credit.

Trophoblastic Disease: Will be part of a new grant application (in preparation).

Colposcopy: A supplemental request for two years funding will be proposed to analyze the impact of colposcopy in the Birmingham Metropolitan area.

Publications: Scott, Lowell K., Shingleton, Hugh M., Hatch, Kenneth D., Maisiak, Richard S., "Evaluation of the impact of a colposcopy satellite clinic," Southern Medical Journal, In Press.

Program Director: Robert T. Bowser, Ph.D.

Grant 24119: Case-control Study of Urinary Cancer in Greater Copenhagen

From 08/01/78 to 01/31/82

FY 81: Est. \$12,700

Dr. O.M. Jensen, Danish Cancer Registry, Strandboulevarden 49, DK 2100 Copenhagen, Denmark

Objectives: By means of population based study of cases and controls the relative risk of developing bladder cancer, cancer of the renal pelvis and ureter will be estimated for occupation, smoking, coffee drinking, consumption of artificial sweeteners, drugs (including analgetics) and certain cosmetics. Attention will be paid to the possible interaction between exposures.

Accomplishments: Data collection started in April 1978. Approximately 420 cases of bladder cancer and some 80 cases of ureter and renal pelvis cancer have been interviewed according to a standard procedure. Cases reported to the study are continuously checked against routine notifications to the Cancer Registry. Some 700 controls drawn at random from the Copenhagen population have been interviewed for control purposes. In addition 3 age and sex matched hospital controls have been interviewed for comparisons with the pelvis and ureter cancer cases. Preliminary analyses of the material collected has started.

Plans: Data collection will continue through June 1981, leaving the following groups for comparisons: bladder cancer cases, ureter and renal pelvis cancer cases, controls from the general population, hospital based controls for pelvis and ureter cases. Results will be available towards the end of 1982.

Program Director: William E. Straile, Ph.D.

Grant CA 24204: Selective Radioimmunotherapy of Colon Cancer

From: 04/01/78 to 03/31/81

FY 81: -0- (Ann. \$88,286)

Dr. David M. Goldenberg, University of Kentucky, 800 Rose St., Lexington, KY 40536

Objectives: The objective is to determine whether tumor-localizing antibodies to carcinoembryonic antigen (CEA) can be used for selective irradiation of CEA-producing tumors of human origin grown in hamsters with slow neutrons by combining a neutron-capturing agent (boron) with the tumor-localizing antibodies. If successful, a new approach in the treatment of CEA-producing human cancers, including colon carcinoma, will be available. The objectives include synthesis of boron-containing compounds capable of combining in sufficient quantities with the anti-CEA IgG without adversely affecting either their solubility or immuno-specificity; and the use of these boron-containing antibodies in conjunction with slow neutron irradiation to selectively kill the neoplastic tissue.

Accomplishments: Three compounds were initially selected as model labelling reagents, however, inconsistent and unreproducible results were obtained in protein labelling experiments. Hence, a major effort was devoted to purification and structural determination of the products at each step of the reaction sequence using nuclear magnetic resonance and vibrational spectra techniques. A new sequence for large-scale preparation of $\text{CH}_3\text{-CB}_{10}\text{H}_{10}\text{C}(\text{CH}_2)_3\text{-CHNH}_2\text{-COOH}$ has been worked out to facilitate microdistribution studies. Techniques and limitations of the system for use on very small samples of tumor tissue are being investigated. Commercial instrumentation has been redesigned to cope with methodological problems.

Efforts to label antibodies to CEA have been successful. Neither the specificity nor the affinity of the antibody has been appreciably altered. The use of CSAP radioantibodies show equal or better tumor localization than CEA antibodies, and a mixture of both antibodies localize GW-39 tumors more effectively than either antibody alone.

Plans: Development of labelling techniques and agents is anticipated. Analytical procedures for the graphite furnace atomic absorption spectroscopy will be established. Attention will be directed at determining radiation protocols; determination of boron localization and microdistribution will receive priority.

Publications: None.

Program Director: Vincent J. Cairolì, Ph.D.

Grant CA 24217: Carcinogens and Mutagens in Colon Cancer

From: 08/01/78 to 07/31/81

FY 81: -0- (Ann. \$70,713)

Dr. John H. Weisburger, American Health Foundation, Naylor Dana Institute for Disease Prevention, 1 Dana Road, Valhalla, NY 10595

Objectives: It is the continuing effort of this program to test the hypothesis that mutagens found in fried meat are the genotoxic carcinogens for colon cancer and perhaps, other nutritionally linked cancers. Isolation, identification, and characterization of the mutagens constitute our major objectives.

Accomplishments: The following key findings have been made: The mutagens in fried meat are, to a large extent, different from those observed during pyrolysis of pure amino acids such as tryptophan. The components in fried meat are somewhat different from those found in fried fish. We have postulated that the Maillard browning reaction may be leading to similar products and we have found this to be so in the analytical systems we have developed. We have devised several novel chromatographic systems in collaboration with Dr. Sugimura and associates in Tokyo to resolve the major mutagenic fractions. We have identified one of these mutagens to be 2-amino-3-methylimidazo[4,5-f]quinoline which sterically resembles the colon carcinogen 3,2-dimethyl-4-aminobiphenyl. We have demonstrated that soy protein inhibits the formation of the fried meat mutagens. Addition of celite does so, too. On the other hand, casein yields more mutagenic activity; and we have found that fat increases the mutagenic activity produced in fried meat.

Plans: We propose to synthesize one of the mutagens isolated from fried meat and to test it for carcinogenicity with emphasis on our hypothesis that the fried meat mutagens may be the genotoxic carcinogens for colon cancer.

We will continue the isolation of the as yet unknown mutagens in fried meat, and we will attempt to determine their mechanism of formation and the possible inhibition of their formation in fried meat.

Publications:

Weisburger, J.H., Reddy, B.S., Fiala, E.S., Wang, Y.Y., Vuolo, L.L., Wynder, E.L., and Spingarn, N.E.: Dietary Factors in the Causation and Prevention of Neoplasia. In Cancer; Achievements, Challenges, and Prospects for the 1980's, J. Burchenal and H. Oettgen, Eds. New York, Grune and Stratton, 1981; pp. 595-613.

Spingarn, N.E., Garvie-Gould, C.T., Vuolo, L.L., and Weisburger, J.H.: Formation of Mutagens in Cooked Foods. I.V. Effect of Fat Content in Fried Beef Patties. Cancer Letts., 12:93-97, 1981.

Spingarn, N.E., Garvie-Gould, C.T., and Vuolo, L.L.: Analysis of Methanol for Reversed-phase Gradient Elution Liquid Chromatography, Analytical Chemistry, 53: 565-566, 1981.

Weisburger, J.H., Reddy, B.S., Spingarn, N.E., and Wynder, E.L.: Current Views on the Mechanisms Involved in the Etiology of Colorectal Cancer. In Colorectal Cancer: Prevention, Epidemiology, and Screening, (Progress in Cancer Research series), S.J. Winawer, P. Sherlock, and D. Schottenfeld, Eds. New York, Raven, 1980; pp. 19-41.

Program Director: Vincent J. Carioli, Ph.D.

Grant 24268: Clinical Cancer Education Program

From 07/01/78 to 06/30/83 FY 81: 167,518
Dr. Montague Lane, Baylor College of Medicine, 1200 Moursund Avenue,
Houston, Texas 77030

Objectives: This program is directed at broadening and intensifying the clinical cancer education of (1) medical students, (2) house officers, (3) clinical associates, (4) practicing physicians and (5) paramedical personnel.

These objectives will be achieved through the development of multidisciplinary training experiences, including lectures introduced into the curriculum, a special lecture series in Oncology, clinical ward assignments, outpatient experiences, tumor clinics, and tumor conferences. New electives will be developed.

Accomplishments: Multidisciplinary clinics have been established in several areas, including a combined medical oncology-radiotherapy clinic, a gynecological oncology combined clinic, a head-and-neck cancer combined clinic, and a urological malignancy clinic. These clinics are attended by practicing physicians, house officers, clinical associates, clinical assistants and medical students on rotations through the various services. Also in attendance at these clinics are paramedical personnel. The core curriculum has been broadened to include many lectures related specifically to clinical oncology. An elective lecture series in clinical oncology has been developed which is multidisciplinary in its presentation. Cancer related lectures are given weekly or every other week in almost every specialty and numerous basic and clinical cancer electives have been developed and then taken by the students. A syllabus has been organized which gives details of all of the cancer education at our institution. Four clinical assistants received support under the grant for electives in pediatric-hematology-oncology and medical oncology. Eleven clinical associates made important contributions to teaching activities relating to many aspects of the program including lectures. Psychosocial problems are given considerable emphasis through a liaison rounding service. The program has been highly successful as evaluated by the performance of clinical associates and student interest measured by participation in credit and non-credit electives and selection of oncology as a field of future endeavor.

Plans: The College is converting from a three-year to a four-year curriculum, which will permit us to develop additional curriculum time in clinical cancer and additional opportunities for clinical assistance to have non-credit electives. The faculty will play a major role in developing clinical experiences for students taking a cancer prevention course.

Program Director: Margaret H. Edwards, M.D.

Grant 24321: Cell Surface Glycoconjugates in Pancreatic Cancer

From 07/01/78 to 06/30/81

FY 81: 0 (Ann. \$60,528)

Dr. Y.S. Kim, Veterans Administration Medical Center and Department of
Medicine, University of California, San Francisco, California 94143

Objectives: There are three main aims of this project: (1) the investigation of the cell surface glycoconjugates of normal and cancerous pancreatic cells and tissues from experimental animals and man using lectins; (2) a comparison of the cell surface membrane glycoproteins and glycolipids of these cells and tissues after external cell surface radioactive labeling; (3) the detection, characterization and purification of tumor-associated glycoproteins and glycolipids. If these aims can be achieved they will provide a basis for the development of methods for the earlier detection of pancreatic cancer. In addition, they may also lead to improvements in the treatment of the disease.

Accomplishments: Because of the lack of a normal human pancreatic cell line with which to compare the results obtained using lines derived from human pancreatic tumors, it was decided to treat the cancer cell lines with differentiating agents to alter their tumorigenicity and to correlate any changes with alterations in the cell surface glycoconjugates. The methods used to study the glycoconjugates were expanded to include not only cell surface radiolabeling but also the role of glycoconjugates in the interaction of the cell with extracellular matrices, the patterns of closely-related surface glycoproteins in growth regulation. A major finding was that differentiating agents greatly reduced or inhibited the tumorigenicity of the cell lines in vitro. In vivo studies of this effect, in nude mice, will be completed by the end of the project as will the studies of the interrelationship between tumor tumorigenicity and cell surface glycoconjugates.

The second area of research under investigation is the antigenic determinants of human pancreatic tumor cell lines. Antibody-producing hybridomas have been formed using two different cell lines as antigens. Monoclonal subcultures of these hybridomas are now being selected using an enzyme-linked immunoassay for cell surface components.

Plans: It is intended to increase the number of differentiating agents and cell lines studied as well as the number of monoclonal antibodies produced. In this way, the precise characteristics of the relationship between cell surface glycoconjugates and human pancreatic cancer will be elucidated.

Publications:

Kim, Y.S., Tsao, D., Hicks, J. and McIntyre, L.J.: Surface membrane glycoproteins of cultured human pancreatic cancer cells. Cancer 47:1590-1596, 1981.

Program Director: William E. Straile, Ph.D.

Grant 24416: Psychological and Familial Precursors of Cancer

From 09/01/78 to 08/31/83 FY 81: \$166,646
Dr. Caroline B. Thomas, Johns Hopkins University, 550 North Broadway
Baltimore, Maryland 21205

Objectives: (1) To identify youthful psychobiological characteristics recorded 19 to 33 years ago on a cohort of 1,337 medical students which preceded the occurrence of cancer; (2) to continue collecting follow-up data on subjects and parents; (3) to identify premorbid psychological profiles of subjects developing cancer; (4) to study the familial incidence of cancer. Our rationale is that human differences in apparently healthy young people have been shown to be potential predictors of premature disease and death from cancer. This approach is significant because it broadens the concept of the determinants of cancer and focuses public health attention on the need for early prevention.

Accomplishments:

1. We have written a manual which defines the scoring methods used in our studies of Rorschach interaction patterns of response (A 5 above).
2. We have derived new factor scales from the Family Attitudes Questionnaire, tested the discriminating power of the factor scales, and investigated the possible role of intervening variables in mediating the previously demonstrated relationship between lack of closeness to parents and cancer.
3. We have reduced and dimensionalized the large data base concerning habits of work and recreation of our subjects in youth.
4. We have completed first phase data gathering concerning the prevalence of cancer in relatives of subjects in our cohort.

Plans: (1) Evaluation of newly-derived habits of work and recreation factor scales; (2) analysis of first phase data concerning cancer prevalence in relatives of cohort subjects; (3) search for psychobiological patterns among subjects who: are living with major cancer (N = 31), died of cancer (N = 20), committed suicide (N = 18), or are living healthy controls.

Publications:

Thomas, C.B., and McCabe, O.L.; Precursors of premature disease and death: Habits of nervous tension. Johns Hopkins Med. J. 147: 137-145, 1980.

Thomas, C.B.: Stamina: The thread of human life. Editorial. J. Chr. Dis. 34: 41-44, 1981.

Duszynski, K.R., Shaffer, J.W., and Thomas, C.B.: Neoplasm and traumatic events in childhood: Are they related? Arch. Gen. Psychiat. 38: 327-331, 1981.

Program Director: Catherine S. Bell, M.S.

Shaffer, J.W., Duszynski, K.R., and Thomas, C.B.: Orthogonal dimensions of individual and group forms of the Rorschach. J. Person. Assess., in press.

Graves, P.L., and Thomas, C.B.: Themes of interaction in medical students' Rorschach responses as predictors of midlife health or disease. Psychosom. Med., in press.

Grant 24426: Clinical Cancer Education Grant

From 07/01/78 to 06/30/84 FY: 81 \$150,992
Dr. Robert J. Lukes, USC Comprehensive Cancer Center
2025 Zonal Avenue, Los Angeles, CA 90033

Objectives: This program is designed to coordinate and enhance the provision of comprehensive and integrated clinical cancer education at the USC School of Medicine. Its primary objectives are curricular enrichment in oncology for undergraduates, and the provision of multidisciplinary continuing education to postgraduate physicians, faculty and staff. The executive Committee achieves these goals through (1) program planning which emphasizes interaction among the nine oncology units, (2) educational activities such as seminars which are multidisciplinary in nature, (3) support of clinical experiences and educational programs in oncology for medical students, and (4) the teaching activities of the Clinical Associates.

Accomplishments: (1) Development of a comprehensive and multidisciplinary educational program in oncology at the USC School of Medicine. (2) Annual appointment of eleven board qualified physicians as Clinical Associates in gynecologic, medical and radiation oncology, hematology, hematopathology, and surgical pathology. These Clinical Associates are then responsible for attending and participating in tumor boards and educational conferences, and for the teaching of residents, interns, and students. (3) Support of fifteen Clinical Assistantships per year for predoctoral studies in preclinical oncology research and clinical experiences in oncology. (4) Coordination and sponsorship of a monthly Oncology Consultants' Seminar series which invites investigators of national stature to present topics in preclinical cancer research and clinical cancer patient management to USC faculty, staff and students. (5) Coordination of weekly Oncology Grand Rounds which are case-oriented multidisciplinary cancer conferences presented by USC faculty and staff to an average audience of fifty members of the faculty, staff, postgraduate physicians, and students. (6) Clinical Electives for two medical students every six weeks in medical oncology and hematology for 3rd and 4th year medical students. (7) Travel support for eleven Clinical Associates which encourages the presentation of scientific papers at major conferences. (8) The CCEP provides guidance to a medical student organization, the St. George Society, which has sponsored six dinner seminars for medical students on clinical topics in oncology during the 1980-1981 academic year. (9) The publication of a monthly Cancer Events Calendar which informs USC faculty, staff, students and members of the medical community of all educational events in oncology occurring at the LAC-USC Medical Center.

Plans: The Clinical Cancer Education Program will continue to provide services and sponsor educational activities which improve and increase exposure to oncology education for USC students, postdoctoral physicians, faculty, and the medical community. This includes maintaining the two Seminar Series and

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Cancer Events alendar, providing fellowship experiences for predoctoral students, and encouraging the teaching activities of the Clinical Associates. The Executive Committee is dedicated to assessing the educational experiences in oncology available at USC and developing new programs when appropriate. Special attention will be placed on improving undergraduate education, and encouraging the collaboration of faculty and Clinical Associates in this process.



From 09/30/75 to 05/31/83

FY 81: est. \$97,734

Dr. M.J. Droller and D. Gomolka, Johns Hopkins University, School of Medicine
Baltimore, Maryland

Objectives: These studies were designed to examine changes in the cellular immune response in an animal model of bladder cancer and to characterize the possible influence of interferon (IF), interferon inducers, prostaglandins (PG), and prostaglandin synthetase inhibitors on this response.

Accomplishments: Purified lymphocytes were prepared with or without monocytes (macrophages) from the peripheral blood or spleens of Fischer rats fed a diet containing 0.2% N- 4-(5-nitrofuryl)-2-thiazolyl formamide (FANFT) or from age-matched controls. For some studies, unstimulated macrophages were obtained from the peritoneal cavity of the same animals prior to lymphocyte harvest. Cytotoxicity was determined by a ⁵¹Chromium-release assay using as targets either a lymphoblastoid mouse cell line (YAC) or a FANFT-induced bladder tumor rat cell line (A_y). Lymphocyte blastogenesis was determined by incorporation of ³H-thymidine in mixed lymphocyte/tumor cell culture. In some experiments, interferon and/or prostaglandin synthetase inhibitors (indomethacin, acetylsalicylic acid) at varying concentrations were added in the cytotoxicity assay. In other experiments, lymphocytes or target cells were preincubated with the same substances prior to their addition to the cytotoxicity assay mix.

A 5-15% depression of lymphocyte cytotoxicity was seen within 6-10 weeks after the onset of carcinogen ingestion. This depression was maintained for the duration of tumor growth and did not appear to be correlated with the ultimate extent of tumor. Interestingly, there did not appear to be any difference between lymphocyte/tumor cell culture.

Separate studies suggested that depression of cytotoxicity did not reflect suppressor cell activity in tumor-bearing animals. Nor did the presence of PG synthetase inhibitors during incubation enhance lymphocyte cytotoxicity in either control or tumor bearing animals, suggesting that tumor cell PG production did not influence these observations that A_y cells produced substantial levels of PGE₂ in response to exposure to effector lymphocytes, and that similar PGE₂ levels had been shown to interfere with the expression of lymphocyte cytotoxicity. It was also of note that monocytes themselves were found to produce PGE₂. However, their presence in the cytotoxicity assay did not appear to prevent lymphocyte cytotoxicity, and the addition of indomethacin to such samples did not appear to augment the degree of cytotoxicity that was seen.

The addition of interferon to cytotoxicity incubation mixtures led to a 10-20% enhancement of the expression of lymphocyte cytotoxicity for both control and tumor-bearing animals. Preincubation studies demonstrated that this effect reflected a direct enhancement of lymphocyte activity rather than the manifestation of a toxic effect on tumor target cells. The degree of enhancement was sufficient to permit the expression of cytotoxicity in

Program Director: William E. Straile, Ph.D.

lymphocytes from tumor-bearing animals to reach those levels of cytotoxicity in lymphocytes from control animals. Thus, effective enhancement in tumor-bearing animals may have been even greater in relative terms than the degree of enhancement seen in control animals. The additional presence of indomethacin during interferon-induced enhancement of cytotoxicity did not augment the total cytotoxicity that was seen, regardless of the presence or absence of monocytes in the assay mix.

In sum, a significant depression of lymphocyte cytotoxicity occurs in animals with FANFT-induced bladder tumors. This appears to reflect decreased activity of potential effector cells rather than their absence. A suppressor cell phenomenon did not appear to account for these observations. Nor did inhibitors of prostaglandin production (either by tumor cells or by monocytes) lead to recovery of activity. However, cytotoxicity could be recovered by exposing effector cells to interferon, a known enhancer of natural killer cell activity and in this setting the degree of activity was similar to that of controls.

Plans: On the basis of these observations, we are presently exploring two areas.

One is based on the assumption that depression of the immune response provides a milieu that is conducive to the progression of tumor; conceivably, prevention of such depression could modify tumor growth. The other is based on the assumption that tumor behavior is independent of any concomitant side effects on the immune response such that manipulations of immune response activity would not be expected to alter tumor progression.

Grant 24644: Development of Computer Based Cancer Profile Programs

From 03/01/79 to 02/28/81

FY 81: 0 (Ann. \$60,000)

Dr. B. T. Williams, Regional Health Resource Center, 1408 West University Avenue, Urbana, Illinois 61801

Objectives: The overall objective of this program is to enhance the productivity of population screening efforts by increasing the yield of true positive results for early detection programs. This will be accomplished by the development of an interactive computer-based screening program designed to calculate individual risk profiles. The profiles will determine the recommendation for and nature of more specific screening, education, or intervention programs to reduce the risk of future disease. This program builds on the existing Health Hazard Appraisal concept.

Accomplishments: The Computer-Based Cancer Profile Program was completed in the following stages: 1) development of an efficient method for reviewing and evaluating the epidemiological literature; 2) selection of appropriate risk factors and calculation of relative risk; 3) development of a methodology for combining multiple risk factors using a multi-factor logistic model derived by the application of contingency table iterative proportional fitting, or "raking," algorithms; 4) adopting the 1976 age (by single year)-, race-, and sex-specific mortality rates as our baseline measure for calculating ten-year survival rates; 5) selection of specific screening tests and recommended frequencies according to the risk level of the individual rather than for age/sex categories. The diseases which are included in the program are: coronary heart disease, stroke, cirrhosis, and cancers of the lung, breast, colon and rectum, cervix, endometrium, prostate, ovary, bladder, skin, stomach and pancreas, and leukemia. For a few of the cancers, no risk factors can be reliably determined: in these cases, only the average mortality rate is shown.

Plans: We are currently seeking funding for program evaluation which will involve a prospective trial with a large population of asymptomatic individuals who will use the program. These data will permit the calculation of prevalence rates for multi-factor risk categories, with this information, and similar information obtained from current patients, we can adjust the screening recommendations to any predetermined level of sensitivity and specificity.

Program Director: Dorothy R. Brodie, M.D.

Grant 24677: Oral/Head-and-Neck Clinical Cancer Education Program

From 07/01/79 to 06/30/82

FY 81: \$47,978

Dr. Fran Watkins, Oklahoma College of Dentistry
Oklahoma City, OK 73190

Objectives: The program is designed to augment a multi-disciplinary program for three major components of care in oral/head-and-neck cancer. These are (1) preventive measures, (2) health promotion, and (3) knowledge and ability to provide diagnosis and treatment for patients with positive diagnostic findings. The program consists of educational activities for dental health professionals and consumers including training, coordination, and information exchange for these groups. The consumer education program will provide information and instruction on self-examination techniques for detection of oral/head-and-neck cancer. Further educational services will be provided through a dental oncology unit. The program also includes a formative approach for the educational activities.

Accomplishments: These include (1) establishment of dental oncology unit for dental management of oral/head-and-neck cancer patients, dental and dental hygiene students rotation, (2) development of Oral Cancer Awareness week in State of Oklahoma, (3) regular community classes for teaching the self-examination classes to interested individuals, (4) coordination with the American Cancer Society and the Oklahoma Dental Association to provide weekly oral/head-and-neck cancer screenings for businesses in Oklahoma, (5) training and assistance to local dental society groups who wish to do screenings in their communities, (6) oral/head-and-neck cancer symposium for dental health professionals, (7) nutritional counseling for oral/head-and-neck cancer patients, (8) workshops on detection and diagnosis of oral cancer, (9) videotapes on Self-Examination for oral cancer and the Psychological Aspects of oral cancer, (10) distribution of oral cancer literature for patients and other segments of the public, (11) development of a summer educational program for 3 dental assistants, and (12) data collection on screenings and self-examination teaching for formative evaluation.

Plans: The focus will be on further development of educational activities and program coordination with other organizations in Oklahoma. Evaluation of the program efforts including the dental oncology unit data, the self-examination teaching activities, oral/head-and-neck screening results and workshop outcomes. Videotapes for teaching materials will also be completed.

Program Director: Margaret H. Edwards, M.D.

Grant 24751: Northern California Oncology Group Education/Demonstration
Program for Community Health Providers

From 04/01/80 to 03/31/81

FY 81: \$596,211

Dr. Stephen Carter, Northern California Oncology Group, Building B,
Suite 355, 1801 Page Mill Road, Palo Alto, California 94304

Objectives: The overall goal of the NCOG Community Outreach Program is to assure the optimal diagnostic evaluation, staging, treatment, and rehabilitation of cancer patients in the participating Northern California Cancer Program regions. Two major programmatic thrusts are being developed toward this goal. First, multidisciplinary clinical committees were formed initially in each of the five participating regions: greater Fresno, Sacramento, greater Reno, the South Bay and the East Bay area. Secondly, a broad range of professional education programs are being developed for physicians, nurses, pharmacists and other medical professionals to complement the protocols and increase the individual's awareness of the most current diagnostic, treatment and rehabilitation strategies and techniques.

Accomplishments: The NCOG Outreach grant was implemented on the first of April 1979. During the first year of this grant, an Outreach Steering Committee composed of the Principal Investigators from each of the five Outreach communities was formed to direct the program. The committee meets on a regular basis. During the last year, an additional clinical committee was established as part of the Greater Contra Costa County Cancer Program (GCCCCP). A part-time Protocol Administrator was hired by the GCCCCP and trained at NCOG headquarters. The GCCCCP has already begun accessioning patients onto NCOG protocols. The Internal Outreach Steering Committee composed of NCCP Cancer Control staff, NCOG staff, and Administration manages internal programmatic details. The Outreach Program Coordinator continues to oversee and coordinate the activities of the Outreach Program. Protocol Activity - The six Outreach Clinical Committees continue to review NCOG protocols as they are activated. The individual committees then decide which protocols they feel are most appropriate for their community. During the second year of the Outreach Program, community physicians placed over 255 patients on NCOG protocols. Community patients now account for approximately 25% of overall NCOG accrual. Quality Control Analysis - The NCOG Statistical Office performed a quality control analysis on NCOG institutional members and NCOG Outreach members. The analysis indicated comparable results on response, toxicity and survival with similar patient populations for the communities and the NCOG participating members. Human Subject Review Committees - NCOG protocols are submitted for human subjects review by community hospitals following approval by the clinical committees. Education - A program on the Multi-disciplinary Treatment and Management of Primary and Metastatic Brain Tumors was conducted in Sacramento and the South Bay. The Oncology Nurse Symposium has been held in the South Bay, Fresno, and Reno. A Leukemia Symposium was developed and held in Reno and the East Bay. The Seminar in Oncology: Focus on Models of Practice was held in the East Bay.

Finally, the Advances in Breast Cancer Therapy Symposium was held in Reno. Group Meeting - The NCOG Group Meeting was held in October 1980 and was attended by over 40 community physicians participating in the NCOG Outreach Program. The community

Project Officer: Harry Handelsman, D.O.

physicians became members of the NCOG Site and Modality Committees and thus are actively involved in protocol development and review. Evaluation - The evaluation of the NCOG Outreach Program is being conducted by the NCOG Statistical Office and the Evaluation team of Drs. Arlene Fink and Jacqueline Kosecoff. During the last year, an evaluation plan for the Outreach Program was developed. The plan will be piloted and implemented during the next year.

Plans: During the third year of this program, we hope to continue increasing patient accrual on NCOG protocols. Toward this end, NCOG Outreach physicians are actively encouraged to participate in NCOG Site and Modality Committees and thus in protocol development. Professional education efforts will be expanded. We will continue multidisciplinary education efforts for particular sites. Anticipated symposia include ovarian cancer and update on breast cancer therapy. Patient education materials from Community Outreach hospitals are being compiled and reviewed. A handbook for pharmacists of Chemotherapeutic Drugs will be distributed and evaluated.

Publications:

Carter, S.: The Challenge of Clinical Research and Community Oncology. Cancer Topics 3: 57-67, 1981

Grant CA 24887: Quinazoline Analogs of Folic Acid Therapeutic Agents

From: 09/30/78 to 08/31/81

FY 81: -0- (Ann. \$31,903)

Dr. Joseph R. Bertino, Yale University School of Medicine 333 Cedar Street, New Haven, CT 06510

Objectives: The long-term objective of this proposal is to develop improved chemotherapy for patients with colorectal cancer. New quinazoline analogs of folic acid found to be potent inhibitors of thymidylate synthetase, a key enzyme in DNA biosynthesis, and inhibitors of growth of the colon carcinoma line HCT-3, and the rectal carcinoma line, HRT-18, will be tested against growth of the mouse colon tumors 38 propagated in vivo. One compound, 5-8-dideazaisofolic acid (IAHQ), has shown excellent activity in these assays, and its mechanism of action and toxicology will be studied prior to human phase I studies.

Accomplishments: Approximately 15 quinazoline antifolates will have been tested as inhibitors of thymidylate synthetase, and as inhibitors of growth of the human colon carcinoma, HCT-8. In addition to IAHQ, one or two promising compounds will be further tested as inhibitors of colon 38 in mice. Radiolabelled IAHQ will be synthesized by Dr. John Hynes, of the University of South Carolina, and studies of this compound will be undertaken. Of significance is the finding that this compound is converted in vitro to polyglutamate forms ($n = 1-3$), and that the triglutamate is a more potent inhibitor of thymidylate synthetase than is the monoglutamate (8 fold).

Therefore, utilizing the radiolabelled compound, we plan to investigate whether this conversion occurs within cells as well. We also expect to complete the pharmacology and toxicology of IAHQ in the mouse, preliminary to large animal toxicology studies, and possible testing (phase I) in man. Before testing in man, we plan to test IAHQ against a panel of human colon carcinoma cells from patient biopsies propagated in the soft agar cloning system.

Plans: Additional analogs will be tested and possibly more potent and or effective compounds will be identified. At this time, a recommendation will be made as to which compound should be tested in man.

Publications:

Fernandez, D.J., Cardenas, R.M., Hynes, J.B., and Bertino, J.R.: Effects of a New Quinazoline Antifolate, 5-8-dideazaisofolic Acid, on Colon Carcinoma. In Folyl and Antifolyl Polyglutamates, J.R. Bertino, B.A. Chabner, and I.D. Goldman, Eds., in press.

Program Director: Vincent J. Cairoli, Ph.D.

From: 09/30/78 to 08/31/81

FY 81: -0- (Ann. \$30,231)

Dr. John B. Hynes, Ph.D., Medical University of South Carolina, 171 Ashley Ave., Charleston, SC 29403

Objectives: The primary objective of this research program involves the synthesis of folate analogues directed toward improved chemotherapy of colon adenocarcinoma. A promising new agent, 5,8-dideazaisofolic acid, (IAHQ) (NSC 289517) is currently being evaluated at the National Cancer Institute as well as at several other laboratories. Chemical modifications of IAHQ are being prepared which may have superior antitumor activity by virtue of altered tissue distribution and/or metabolism. The introduction of substituents at position 5 such as methyl or halogen as well as alkylation at N-9, has received high priority. The preparation of several of these new modifications as well as certain γ -L-glutamyl derivatives constitutes a significant synthetic achievement.

Accomplishments: IAHQ as well as related quinazoline analogues of folic acid have been shown to be substrates of mammalian folyl polyglutamate synthetase. It is probable that these compounds are also altered in an analogous manner *in vivo*. Therefore, γ -L-glutamyl derivatives of four of the most effective inhibitors of L1210 leukemia thymidylate synthetase were synthesized for enzyme inhibition and metabolic studies. The resynthesis of 5-methyl-5, 8-dideazaisofolic acid was accomplished using a new route, while the corresponding 5-chloro modification was prepared using a novel multistep synthetic sequence. Considerable progress has been made in the area of the 5-fluoro and N-9 methyl modifications of IAHQ, and the target compounds should be completed shortly. A large quantity of IAHQ was prepared and made available to the National Cancer Institute for the tumor panel as well as for further biological, toxicological, and immunological studies. Approximately seven additional quinazoline analogues of folic acid have been prepared and each of these is currently being evaluated biochemically and biologically.

Plans: The synthesis of new folic acid modifications suggested by the collaborative biological studies being conducted at Yale University will be continued. The completion of compounds described in the preceding section will be performed and poly- γ -L-glutamyl modifications will be elaborated as warranted by *in vitro* antitumor evaluation. Precursors for formation of isotopically labeled IAHQ (^3H) will also receive priority.

Publications: None.

Program Director: Vincent J. Cairoli, Ph.D.

From: 04/01/79 to 03/31/81

FY 81: -0- (Ann. \$95,486)

Dr. Steven R. Tannenbaum, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02189

Objectives: The objectives of this project are to explore whether nitrite and N-nitroso compounds are causally implicated in the etiology of intestinal cancer in man, and/or whether the intestinal tract can serve as a site for the synthesis of N-nitroso compounds. In order to pursue these objectives, studies will be conducted on nitrate metabolism in man and in the rat. These studies will include variations in the diet which alter the state of the intestinal tract (e.g., increased dietary fiber) or addition of compounds which may react with nitrite, such as ascorbic acid.

Accomplishments: Studies with $^{15}\text{NO}_3^-$ in the germ free and conventional rat show that there is endogenous synthesis of NO_2^- which is independent of the gastrointestinal (GI) flora. Thus, nitrate synthesis appears to be a mammalian process, and the normal microflora has been eliminated as an obligatory component of nitrate production. However, the same experiment also disclosed that in rats fed $^{15}\text{NO}_3^-$, nitrate is recycled into the lower GI tract. In the germfree animals it appears as fecal $^{15}\text{NO}_3^-$, but in the conventional rat it is converted to $^{15}\text{NH}_3$ which ultimately appears as ^{15}N -urea in the urine. The urine of the germfree rat is devoid of ^{15}N -urea. Thus, systemically distributed nitrate is cycled through the colon and may have the capacity to lead to the synthesis of N-nitroso compounds.

Plans: Studies to elucidate the possible involvement of N-nitroso compounds in large bowel cancer will be continued.

Publications:

Green, L.D., Tannenbaum, S.R., and Goldman, P.: Nitrate Synthesis in the Germfree and Conventional Rat. Science, 212:56-58, 1981.

Ralt, D., Gomez, R.F., and Tannenbaum, S.R.: Conversion of Acetohydroxamate and Hydroxylamine to Nitrite by Intestinal Microorganisms. Euro. J. Appl. Microbiol. Biotech., in press.

Program Director: Vincent J. Cairoli, Ph.D.

From 09/30/78 to 08/31/81

FY 81: \$0 (Ann. \$119,219)

Dr. A. Wayne Meikle, Department of Internal Medicine, University of Utah
College of Medicine, 50 North Medical Drive, Salt Lake City, Utah 84132

Objectives: The possible contribution of familial (genetic), endocrine and environment risk factors on the development of prostatic cancer are being studied in men of the intermountain region. Our postulate is that the high rate of prostatic cancer observed in Mormon men of Utah may be caused by an interaction of the various risk factors.

The objectives are to determine whether: (1) The plasma concentration of sex-steroids and prolactin are abnormal in untreated probands (men who develop the cancer before age 62), and first-order relatives as compared to controls of similar age; (2) the plasma content of sex-steroids and prolactin may be affected by familial factors; (3) the risk of the development of the cancer is higher in first-order relatives of the index cases than in age-matched in-law controls; and (4) the prevalence of some apparent epidemiologic risk variables are observed more commonly in probands and their first order relatives than in age-matched controls.

Accomplishments: Approximately 200 additional subjects will be entered into the study during the third year of the investigation. The complete analysis of data on over 1000 individuals entered into some aspects of the study will be completed. The data on the influence of familial factors on the plasma content of sex-steroids has been presented to the Western Society for Clinical Research, and manuscript of the report has been previously accepted for publication. At the National meeting on clinical research, observations that prostatic cancer and plasma sex-steroid levels are strongly affected by familial factors will be presented. Of the 158 probands studied thus far, we have established that 16 of their brothers have prostatic cancer as compared to 2 of their brothers-in-law of comparable age. In addition, 15 fathers of the cases had prostatic cancer as compared to 6 fathers-in-law. Thus, familial factors are the strongest influences ever established for predisposing to the development of prostatic cancer. The data are in manuscript form which has been submitted for publication. Data on environmental risk factors will be analyzed, summarized and submitted for publication. A portion of the data on familial risk for prostatic cancer will be presented to the State Medical Society's Annual meeting.

Plans: We plan to complete (1) the data collection; (2) the detailed analysis of the observations; and (3) the publication of the observations. We also plan to extend the observations to determine possible modes of inheritance that result in the development of prostatic cancer and in the plasma content of sex-steroids. Criteria will be established to suggest careful reevaluation of men who are at elevated risk for development of prostatic cancer.

Publications: Meikle, A.W., and W.M. Stanish: Familial Effects on Prostatic Cancer and Plasma Testosterone Content. Clin. Res. 29:548, 1981.

Program Director: Andrew Chiarodo, Ph.D.

Meikle, A.W., Stanish, W.M., Edwards, C.Q., and Bishop, C.T.: Hereditary Effects on Plasma Content of Sex-Steroids in Man. Clin. Res. 29:84, 1981.

Meikle, A.W., Stanish, W.M., Edwards, C.Q., and Bishop, C.T.: Familial Effects on Plasma Sex-Steroid Content in Men: Testosterone, Dihydrotestosterone and Sex-Hormone Binding Globulin. Metabolism (1981). In Press.

Meikle, A.W., Collier, E.S., Middleton, R.G., and Fang, S-M: Supranormal Content of 5α -Dihydrotestosterone in Benign Hyperplastic Prostate of Humans. J. Clin. Endocrinol Metab. 51:945, 1980.

From 09/30/78 - 08/31/84

FY 81: Est. \$127,374

Dr. B.U. Pauli, Rush Medical College, Chicago, Illinois

Objectives: Tumor invasion is a consequence of the enzymatic breakdown of extracellular matrices, and the infiltration of proliferating tumor cells into the areas of matrix destruction. In the bladder, this process may be regulated, at least in part, by an anti-invasion factor (AIF) which is present in the normal mucosa and submucosa. This factor is salt-extractable and contains potent inhibitors of proteolytic enzymes (i.e. trypsin) as well as an anti-proliferative activity directed against invasive cells. The objective of this project is to study in vitro the regulation of tumor invasiveness by bladder-derived AIF, utilizing defined noninvasive, invasive, and metastatic carcinoma cell lines.

Accomplishments: FANFT carcinoma cells with different invasive potentials were grown in vitro on various extracellular (collagenous) matrices, i.e. tendon, hyaline cartilage, anterior lens capsule, from which the anti-invasion factor had been removed by salt-extraction. As monitored by thin-section electron microscopy, extracted matrices were readily penetrated by invasive and metastatic rat bladder carcinoma cells. The metastatic cell line could be differentiated from the invasive, non-metastatic cell line by its greater depth of invasion. In contrast, noninvasive carcinoma cells and normal bladder epithelial cells lacked the capacity to erode and penetrate extracted extracellular matrices. Invasion by malignant bladder carcinoma cells into extracted matrices was however abolished when low concentrations of bladder-derived AIF were added to the culture medium. AIF appeared to regulate tumor invasion in this system by inhibiting matrix-degrading enzyme activities as well as proliferation and migration of malignant FANFT carcinoma cells.

Biochemical analyses of AIF led us to attribute the anti-invasive activities to a spectrum of proteins with a molecular weight between 6,000 and 50,000 daltons. SDS-PAGE revealed that AIF consisted of 6 major protein bands. It expressed strong tryptic and chymotryptic inhibitory activities. Immuno-diffusion and electrophoretic mobility assays showed that this proteinase inhibitory activity was derived from bladder tissue and not from the serum. The proteinase inhibitor was similar to that of the commercially supplied pancreatic trypsin inhibitor (Trasylol^R). In endothelial cell cultures, AIF inhibited cell proliferation and caused flat growing, potentially invasive endothelial cells to change their shape to non-migratory spindle cells after a 24 hr. exposure, and induced extensive bleb formation and cytolysis after a 48 hr. exposure.

Bladder-derived AIF is currently fractionated in our laboratory, using various chromatographic and electrophoretic steps. Subfractions will be analyzed by various morphologic and biochemical assay methods for their role in the regulation of tumor invasion. These studies focus on a) the inhibition of matrix-degrading proteolytic enzymes, and b) the inhibition of proliferation of malignant cells.

Program Director: William E. Straile, Ph.D.

Publications:

Weinstein, R.S. and Pauli, B.U.: Cell Relationships in Epithelia.
In: Developments in Clinical Cytology. L.G. Koss and D.V. Coleman (eds);
Butterworth & Co., London, Vol. I; 160-180, 1980.

Pauli, B.U., Anderson, S.N., Memoli, V.A. and Kuettner, K.E.: The Isolation and Characterization In Vitro of Normal Epithelial Cells, Endothelial Cells and Fibroblasts from Rat Urinary Bladder. Tissue and Cell 12:419-435, 1980.

Pauli, B.U., Anderson, S.N., Memoli, V.A. and Kuettner, K.E.: Development of an In Vitro and In Vivo Epithelial Tumor Model for the Study of Invasion. Cancer Research 40:4571-4580, 1980

Alroy, J., Pauli, B.U. and Weinstein, R.S.: Correlation between Desmosome Ultrastructure and Tumor Aggressiveness in Human Urinary Bladder Transitional Cell Carcinoma. Cancer 47:104-112, 1981.

Pauli, B.U. and Weinstein, R.S.: Structure of Gap Junctions in Culture of Normal and Neoplastic Bladder Epithelial Cells. Experientia 37:248-250, 1981.

Grant 25064: Pancreatic Carcinogenesis: Role of Duodenal Reflux

From 09/30/78 to 08/31/81

FY 81: 0 (Ann. \$71,916)

Eugene P. Dimagno, M.D., Mayo Medical School, Rochester, Minnesota 55901

Objectives: The long-range goals of this proposal:

1. to determine what physiologic or pharmacologic events or chemicals influence pressure relationships between the duodenum and pancreatic duct that might favor reflux of duodenal contents into the pancreatic duct; and
2. to determine if carcinogens can reflux from the duodenum into the pancreatic duct and induce pancreatic carcinogenesis.

Accomplishments: To investigate the hypothesis that reflux of duodenal contents into the pancreatic duct may be related to pancreatic carcinogenesis, we have used our canine model to simultaneously quantify duodenal volume flow, pancreatic and duodenal pressures, reflux of duodenal contents into the pancreatic duct, and obtain pure pancreatic juice. In the dog, we have found that:

1. pancreatic and biliary secretions during fasting are cyclical and related to the interdigestive motor complex (IDMC);
2. reversal of duodenal to pancreatic duct pressure occurs during phase III of the IDMC and during the second postprandial hour;
3. small amounts of duodenal content reflux into the pancreatic duct postprandially, but reflux is inconsistent during fasting;
4. hormones (secretin, CCK, glucagon, neurotensin) which have different effects on duodenal motility and pancreatic secretion do not alter the normal pancreatic duct to duodenal pressure gradients which suggests the presence of a competent sphincter mechanism that prevents duodenopancreatic duct reflux;
5. nicotine (a) increases duodenal motility and pancreatic secretion by shortening the length of phase I (no motility and minimal secretion) during fasting, and (b) increases postprandial duodenal motility and inhibits pancreatic bicarbonate and trypsin secretion, but does not increase duodenopancreatic reflux;
6. intragastric ethanol and hypertonic glucose increase pancreatic bicarbonate output, duodenal motor activity, duodenopancreatic reflux, and reduces bile acid output;
7. during fasting and postprandially polar metabolites of ^{14}C -1,2 benzanthracene are secreted into the duodenum of the dog in conjunction with peaks of pancreaticobiliary secretion; and
8. metabolites of benzanthracene are secreted into pancreatic juice rather than being refluxed into the pancreatic duct from the duodenum.

Program Director: William E. Straile, Ph.D.

In addition, we have extended these studies to the human where we have developed a gastroduodenojejunal intubation method for measurement of gastric, biliary and pancreatic secretion and gastrointestinal motility. The relationship of the interdigestive pattern of upper gastrointestinal secretion and motility is similar to the dog and that cigarette smoking has similar effects on motility as nicotine in the dog.

Plans: We plan to:

1. determine in the dog if alteration of the interdigestive state by nutrients, nicotine, alcohol, coffee, caffeine, neural agonists and antagonists influences carcinogen metabolism or secretion by the upper gastrointestinal tract;
2. characterize the uptake and storage of benzanthracycline and its metabolites and other carcinogens in gastrointestinal organs, particularly the pancreas, and their secretion into body fluids in relationship to the secretory states of the dog; and
3. determine if cigarette smoking or coffee alters interdigestive and postprandial upper gastrointestinal motility and gastric pancreaticobiliary secretion in man.

Publications:

Hendricks, J.C., DiMagno, E.P., Go, V.L.W. and Dozois, R.R.: Reflux of duodenal contents into the pancreatic duct of dogs. J. Lab. Clin. Med. 96:912-921, 1980.

DiMagno, E.P., Hendricks, J.C., Dozois, R.R., and Go, V.L.W.: Effect of secretin on pancreatic duct pressure, resistance to pancreatic flow, and duodenal motor activity in the dog. Dig. Dis. Sci. 26:1-6, 1981

Grant 25117: Community Radiation Oncology Program - USC

From 07/01/79 to 06/30/82 FY 81: \$171,873
Dr. F. W. George III, University of Southern California, 2025 Zonal Avenue
Los Angeles, California 90033

Objectives: The Community Radiation Oncology Program (CROP) is a community outreach program of the Los Angeles County/University of Southern California Comprehensive Cancer Center (LAC-USC CCC). The objectives of CROP are to develop and implement an integrated program of activities that provide rapid translation of recent advances in oncology to the management of cancer patients using the radiation oncologist as a viable focus for implementing the program in individual institutions. The objectives are accomplished through activities that increase the skills, knowledge, and capabilities of the radiation therapy community (including physicians, nurses, physicists, and technologists), and bring together radiation therapists and other specialties and disciplines in multidisciplinary cancer management efforts.

Accomplishments: A structure survey of 75 radiation oncology facilities in the Southern California region showed that a total of 18,699 new patients were treated in CROP facilities in 1979. It appears that approximately 46% of all patients treated by radiation therapy in California in 1979 were treated in CROP facilities and a total of 124 radiation oncologists practice in CROP facilities, 91 of which are full time radiation oncologists.

The development of process-outcome survey questionnaires were expanded to include questions on the results of clinical and diagnostic tests to determine the disease-free and complication-free survival rates, overall survival rates, and local control rates by stage of disease as well as the frequency with which diagnostic and treatment procedures are used in the care of patients. Collection of diagnostic test results will permit analysis of the efficacy of these tests and the analysis of questions about the utilization of any particular test within the CROP facilities will be more meaningful to clinicians.

The "Radiation Therapy Technologist and Paraprofessional Development Program" has undertaken a needs assessment survey for Medical Dosimetrists in the CROP area to evaluate the need for a Medical Dosimetry School at USC. A preliminary evaluation of the completed questionnaires indicates a strong interest in the Medical Dosimetry School among the technologists and physicians in the CROP network.

During the past year, this program has also sponsored a total of twenty-three seminars and workshops for radiation therapy technologists. These programs have included presentations on the technical and radiation safety aspects of brachytherapy, the design and use of templates and special accessories, hyperthermia equipment and procedures and quality assurance protocols for equipment and isotope calibration, and other important technical issues in radiation oncology.

The professional development program includes a weekly director's conference and weekly seminars in radiation oncology. Monthly seminars entitled

Program Director: Margaret E. Holmes, Ph.D.

CROP also has a "Radiation Oncology Development for Community Hospitals Program", the purpose of which is the enhancement of cancer patient management in the community setting by providing resources essential in the clinical application of new techniques and technologies.

Plans: Program plans for the coming year include completion of the Process-Outcome Surveys and the efficacy study of diagnostic procedures; expansion of the Computerized Registry Information Service and an analysis of the pooled data from this registry; repetition of the Structure Survey; increased network participation in Phase I-IV protocol studies and expansion of the scope to include other groups; enhancement and expansion of the hyperthermia program and extension to more community patients and facilities; extension of the Community Radionuclide and Accessory Demonstration program for optimization of brachytherapy; activation of the Medical Dosimetry Training Program; formalization of the planning program for Radiation Oncology Nursing; and analysis of CROP methodology and documentation in exportable modules.

Grant CA 25136: Molecular Mechanisms in Large Bowel Carcinogenesis

From: 06/01/76 to 12/31/81 FY 81: \$83,007
Jen Fu Chiu, Ph.D., Department of Biochemistry, The University of Vermont,
College of Medicine, Given Building, Burlington, Vermont 05405

Objectives: The objectives of this proposal are to better understand tissue specific nuclear proteins - DNA association in chromatin and to identify specific non-histone proteins and genome segments responsible for the expression of the malignant phenotype. We will attempt to determine whether specific chromatin structure and components are related to transcriptional control of tumor specific genes.

Accomplishments: Tumor-specific antisera against rat large bowel carcinoma dehis-tonized chromatin were produced. These antisera were tissue and tumor specific; they reacted only with chromatin isolated from rat large bowel adenocarcinoma and not with chromatins isolated from other tumors or normal rat colon. Tumor-specific nuclear antigen appeared in the early stages of chemically-induced colon carcinogenesis. At these stages, there are no other observable nuclear or cyto-plasmic alterations in the colon mucosa.

A tumor promoter, sodium barbiturate, in conjunction with the carcinogen, induced higher levels of nuclear antigen activity than that obtained with carcinogen alone. However, carcinogen inhibitors (disulfiram and butylated hydroxytoluene) can abolish the tumor-specific immunoactivity of chromatin. The tumor specific antigen is a fraction of tightly DNA-binding nonhistone proteins which form a complex with DNA. By using protein blotting and immunolocalization techniques, we can determine one protein which seems to be the principal antigen.

The DNA polymerase α activity of colonic epithelial cells increased dramatically after 1,2-dimethylhydrazine (DMH) treatment. The DMH-treated colon mucosa show the presence of a subspecies of DNA polymerase α . The level of polymerase α in colon nuclei increases during chemical carcinogenesis. The misincorporation of noncomplementary deoxyribonucleoside triphosphates by nuclear DNA polymerase increases after DMH treatment. The rise in infidelity of DNA polymerase α in DMH-treated colon is probably due to the increased number DNA polymerase α in DMH-treated rat colon nuclei.

Plans: The immediate plans for this project are to produce specific antisera against nonhistone chromosomal proteins associated with transcriptionally active chromatin from chemical carcinogen-treated cells; to study the interaction of specific antigen and DNA; and, to use specific antisera to identify cells committed to carcinogenesis.

Publications:

Pumo, D.E., Gootnick, D., Little, B.W., and Chiu, J.F.: Colon Tumor Specific Nuclear Antigen with Potential as a Pre-Tumor Diagnostic Probe. Cancer Lett., 9:285-291, 1980.

Chiu, J.F.: DNA Binding Proteins and DNA Synthesizing Enzymes in Eukaryotes. Biochemistry and biology of the Cell Nucleus, Vol. 111, L.S. Hnilica Ed., in press.

Program Director: Vincent J. Cairoli, Ph.D.

From: 07/15/79 to 06/30/82

FY 81: \$95,652 (est.)

Dr. James E. Enstrom (Dr. Lester Breslow, former P.I.), School of Public Health, University of California, Los Angeles, 405 Higgard Avenue, Los Angeles, CA 90024

Objectives: The overall objective is to better understand the etiology of colorectal cancer through the epidemiologic study of low-risk California Mormons and through correlation of available health and nutrition survey data with colorectal cancer mortality data for distinct subgroups of U.S. and California whites. These findings should show how several specific health and dietary habits are related to colorectal cancer risk within the United States. By studying active Mormons we are quantifying and understanding a U.S. population which is actually experiencing a low rate of colorectal cancer, as well as a low rate of total cancer and total mortality.

Accomplishments: Based on 19 years of church records, the 1960-78 standardized mortality ratio (SMR) for active California Mormon males compared with 1970 U.S. whites is as follows: 65% for colon cancer, 41% for rectum cancer, and 59% for colorectal cancer. The SMR for Mormon males and females as a whole is 65-70%. The SMR values are substantially lower than those observed in typical nonsmokers, but similar to those in Seventh-Day Adventists. A prospective study of active California Mormon adults (5,400 High Priests and 4,600 wives) was begun in fall 1979 using lifestyle questionnaires. An additional source, the Spring 1977 USDA National Food Consumption Survey, consists of persons residing in Utah and persons not using coffee, tea, or alcohol. There are no substantial differences between active Mormons and other whites with respect to several major nutrients, such as daily intake of calories, fat, protein, carbohydrates, and dietary cholesterol. However, Mormons appear to consume somewhat more milk, fruits, sugar, and dietary supplements; and, in accordance with church doctrine, they use no coffee, tea, alcohol, or tobacco. The 1971-74 U.S. Health and Nutrition Examination Survey (HANES) and Spring 1977 USDA Survey data tapes are now being used for a correlation analysis of dietary and health factors with U.S. colorectal cancer mortality rates by place of residence and other demographic criteria to test dietary hypotheses. There is essentially no correlation between average dietary fat intake and colorectal cancer death rates in 64 geographical areas within the United States.

Plans: 1979-80 mortality followup will be conducted on the 10,000 active California Mormons using church and state death records. Extensive comparisons will be made among various subgroups of Mormons, along with Seventh-Day Adventists, and Hispanics. Correlation analyses using HANES and USDA nutrition data and U.S. cancer rates will be completed.

Publications:

Enstrom, J.E.: Health and Dietary Practices and Cancer Mortality Among California Mormons. In Banbury Report 4: Cancer Incidence in Defined Populations, J. Cairns, J.L. Lyon, and M. Skolnick, Eds. Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, 1980; pp. 69-90.

Enstrom, J.E.: A Reassessment of the Role of Dietary Fat in Cancer Etiology, *Cancer Res.*, 41, in press, 1981.

Program Director: Vincent J. Cairoli, Ph.D.

Grant 25271: Pediatric Cancer Control: School and Nursing Outreach

From 5/1/79 to 4/30/82

FY 81: \$85,315

Dr. Nancy Cairns, University of Kansas Medical Center, Kansas City,
Kansas 66103

Objectives: Advances in pediatric cancer therapy have enabled most children with cancer to return to their homes, schools, and communities. Childhood cancer has become a chronic disease which need not prevent a child from living a normal or near-normal life much of the time. Therefore, total treatment demands that we look at not only the length of survival with cancer but also the quality of the child's life after diagnosis. The purpose of the proposed project is to develop and evaluate a model for utilizing existing community resources to facilitate the child's rehabilitation. Two community agencies, the county health department and the school system, will be the focus of the efforts of the pediatric cancer control team.

Accomplishments: A pediatric cancer control team (PCCT) has been formed consisting of a pediatric oncology nurse, a pediatric clinical psychologist, a special education teacher certified for grades kindergarten through 12, and support personnel. Sixty-five children have been enrolled in the school intervention program. Twenty school visits and 25 school conference calls have occurred on behalf of these children, with intensive follow-up for five children who are having problems. Inpatient school has served an average of 4.5 children daily.

Evaluation of the academic progress of study children in the 1979-80 school year revealed no significant differences in attendance or grades despite the fact that the study group patients were more seriously ill than were the control patients. Parent and teacher questionnaires indicated satisfaction with and benefit from the intervention program.

Twenty-six patients have been referred to community health nurses and 13 patients are enrolled in the control group for this aspect of the study. Data on the nursing care provided, patient contacts at the cancer treatment center and in the local community, and the quality and cost of care reveal fewer cancer center contacts for study group patients and fewer medical expenses. Quality of care is comparable for both groups.

At the request of the nursing supervisors, the PCCT has conducted one-day workshops in five of the six public health nursing districts in Kansas. Evaluations of the workshops have been positive: overall, 92.5% of attendees rated the workshops as "excellent" or "above average." Analysis of pre- and post-workshop questionnaires indicated significant increase in knowledge of childhood cancer among attendees.

The validity and reliability of nursing questionnaires has been demonstrated by pediatric staff nurses at the University of Kansas Medical Center.

Plans: At the end of the school year, data from the -01 and -02 years of intervention will be evaluated. The PCCT will conduct a limited number of structured interviews to explore parents', teachers' and nurses' perceptions of the intervention program.

Program Director: Janet L. Lunceford, R.N., M.S.N.

Publications:

Cairns, N.U., Klopovich, P., Moore, R., Stephenson, L., Fried, P., Gradolf, B., Suenram, D., Kurz, L., and Butterfield, G. The dying child in the classroom. Essence, Vol. 4, No. 1, 1980, 25-32.

Klopovich, P. and Cairns, N.U. A common sense approach to caring for children with cancer: The community health nurse. International Journal of Cancer Nursing. June, 1980, 3:201-208.

Klopovich, P., Vats, T.S., Butterfield, G., Cairns, N.U., and Lansky, S. School phobia. The Journal of the Kansas Medical Society, Vol. 82, No. 3, 1981 125-127.

Grant 25280: Educational Approaches to Endometrial Cancer Control

From 09/01/80 to 08/31/83

FY 81: \$111,366 (Estimated)

Dr. Susan J. Standfast, New York State Department of Health, Albany, New York
12237

Objectives: This project aims to reduce the incidence of endometrial cancer in a selected area of upstate New York by increasing awareness among the medical community of the risk of endometrial cancer associated with the use of menopausal estrogen therapy and promoting a more judicious use of estrogens. Secondly, this project seeks to improve early detection rates of endometrial cancer through increasing physicians' and women's knowledge of effective screening techniques and the importance of careful follow-up of high risk women. A corollary objective is to increase professional and public understanding of the menopause as a natural developmental stage. Measurements of objectives will be accomplished through before-and-after surveys of physicians and pharmacies.

Accomplishments: During October and November 1980 a professional task force of 12 local opinion leaders was organized. At the first meeting, held in December, educational needs for clinicians and effective methods to meet these needs were identified. A pilot version of the pretest survey of physicians was mailed out in February to 118 physicians outside the study area. As of April 7, 60 had been returned. Suggestions for revision were made by the task force at their second meeting in late March and the main survey was mailed out to 500 study and 500 control area physicians. A draft questionnaire of the population survey of women ages 40-59 has been prepared. Information has been obtained on several survey firms preparatory to soliciting bids in April. The telephone interviewing should take place in June. For the pharmacy survey, exploratory talks have been held with the New York State Pharmacy Board and faculty at the Albany College of Pharmacy. The survey is planned to coincide in time and place with the physician survey. A teaching day for physicians and nurses entitled "Controversies in the Management of the Menopause" has been scheduled for November 19, 1981, at the Albany Medical College. The program is being planned in cooperation with the Departments of Obstetrics and Gynecology, Family Practice, Medicine and Nursing. Two planning sessions have been held with the media specialists to initiate development of patient education materials. A booklet on the menopause has been drafted.

Plans: The second year will be devoted to the conduct of the educational campaign in the study area and monitoring of educational activities in the control area. During the third year the post-test surveys of physicians and pharmacies and a survey of endometrial cancer patients will be conducted. Data from all surveys will be analyzed and the results and conclusions written up for publication.

Program Director: Andrew F. Hegyeli, D.V.M., Ph.D.

Grant 25289: Measuring Physical Function in Cancer Rehabilitation

From 05/01/79 to 07/30/81 FY 81: 0 (Ann. \$80,954)
Dr. Prakash L. Grover, Fox Chase Cancer Center, 7701 Burholme Avenue,
Philadelphia, Pennsylvania 19111

Objectives: To clarify the concept of physical function, validate the unity of this concept across rehabilitation professions, develop a rationally based and empirically meaningful scoring system to enable more uniform measurement of cancer rehabilitation outcomes.

Accomplishments: During the first phase of this study, questionnaires were mailed to 242 physiatrists, 529 occupational therapists, 1,177 physical therapists and 338 rehabilitation nurses. These practitioners were employed in 284 rehabilitation facilities, including 29 affiliated with cancer institutes. 1,204 questionnaires were completed and returned. Data yielded by the first survey supported the hypothesis that there is underlying unity in the concept of physical function among the four types of rehabilitation professionals. These data also provided a minimal list of activities and tasks to constitute a measure of physical function as well as a scale for assessment of the tasks.

In the 2nd phase, using the method of paired comparisons, questionnaires were developed to establish a metric for the scale on which to assess functional tasks. They were addressed to 1088 rehabilitation practitioners. As of 3/31/81, 694 completed responses had been received.

Plans: Data from the second survey will be used to establish a metric for the measurement scale. In addition, methods will be explored for aggregating scores on individual tasks and activities in order to arrive at an overall score of physical functioning which could be used for purposes such as planning treatment, establishing prognosis and evaluating treatment outcomes. The study is expected to be completed according to schedule.

Program Director: Lawrence D. Burke

From 07/01/79 - 06/30/82

FY 81: \$167,363

Dr. C. Ralph Buncher, University of Cincinnati Medical Center,
Eden and Bethesda Avenues, Cincinnati, Ohio 45267

Objectives: The overall goal of the grant is to lower the mortality rate in the Greater Cincinnati area to the level of the national average. To accomplish this goal we have two objectives: (1) to establish an environmental/occupational cancer prevention program in cooperation with Cincinnati's industry, promoting detection of potential environmental causes of cancer, worker education, outreach to industrial health professionals, and worker rehabilitation; and (2) to plan and establish, in cooperation with the major community health professionals, the academic community, and key community and public organizations, a comprehensive program focusing on the continuum of cancer care and stressing those programs which encourage the development of basic community resources in optimal multidisciplinary cancer patient management.

Accomplishments: (1) Project staffing has been streamlined to maximize efficiency. (2) An industrial hazards survey has been implemented in twelve companies and fifteen more surveys will be completed by end of year -02. (3) Wellness fairs and cancer education programs, based on health beliefs and health behavior changes, have been carried out in industrial settings. (4) A cancer rehabilitation resource directory has been compiled for the greater Cincinnati area. (5) Industrial nurses were trained to teach breast self-examination. (6) Numerous professional education seminars and workshops were held, including "Pharmacy and the Cancer Patient", "Cancer of the Breast and Cervix: Current Concepts in Diagnosis and Treatment", "Basic Oncology Nursing Concepts", "Coping with Cancer: Care of the Caregiver", "Caring for the Cancer Patient: A Comprehensive Approach to Discharge Planning", and "Cancer Information: An Update for Occupational Health Professionals". (7) Two industries were consulted about initiating on-site cancer prevention and detection programs. (8) Patient management guidelines for breast cancer were developed. (9) Progress has been made in community-wide planning for future cancer resource needs. Cancer planning committees have met in each of the four subareas to assess current cancer intervention strategies and to plan for augmenting services where appropriate. Study of the high cancer mortality rate among Cincinnati's Black citizens continues, and intervention strategies are being considered by a special cancer study committee. (10) To facilitate communication of grant project investigations, and to share the results of staff efforts with the medical and lay community, a newsletter is published on a monthly basis. In addition, a volunteer speaker's bureau is being organized to educate interested community groups about cancer control.

Plans: (1) Continue long-range planning. (2) Implement community-based cancer prevention & detection programs. (3) Promote tumor boards, investigate use of two-way cable TV for case review outreach to distant community hospitals, and publish article on development of tumor boards. (4) In-depth seminars on most-requested aspects of cancer nursing. (5) Joint research with the University of Cincinnati Psychology Department on psychological roadblocks to breast self-examination. (6) Complete other grant projects.

Program Director: Margaret E. Holmes, Ph.D.

Grant 25402: Complications of CNS Prophylaxis in Childhood Acute
Lymphocytic Leukemia

From 05/01/79 to 04/30/83

FY 81: \$8,171

Dr. Arnold Freeman, Department of Radiation, Roswell Park Memorial Institute,
Buffalo, New York 14263.

Objectives: This study continues to retrospectively evaluate the effects of CNS prophylaxis in approximately 120 children treated on Group B protocols for acute lymphocytic leukemia (ALL) who remain in disease-free remission from one to 11 years. The CNS regimens employed were: (1) IT Methotrexate (2) IT Methotrexate plus cranial irradiation (CRT), (3) IT plus intermediate dose IV Methotrexate. Data is being gathered at four centers using neurological, psychological, psychometric, and intelligence tests, EEG, CAT scan and endocrine evaluation. The evaluators in the above areas are unaware of the type of CNS prophylaxis that was administered.

Accomplishments: Approximately 100 patients have been evaluated, and analysis indicates that Groups 1, 2 and 3 (above) have similar distribution of age, sex, etc. The findings now indicate a higher incidence of EEG abnormalities (p .05) in those patients who received intermediate dose Methotrexate (IDM) (Group 3), but no proven increase in convulsive disorders. The growth hormone levels are significantly lower (p=.01) on CRT patients (Group 2). To date, this has not been translated into decelerated growth in these patients. The CRT patients also did significantly worse on both their verbal (p .05) and performance IQ's (p .01). The IDM appears to be approaching statistical significance in scoring lower on verbal IQ (p=.07), when compared with IT Methotrexate alone. There was also a non-statistical increase of modest abnormalities in CAT scan noted in the CRT group.

Plans: We plan to re-evaluate these patients on three additional occasions over three years to determine if the CNS deficits worsen during this course of time.

Program Director: Donald N. Buell, M.D.

From: 07/01/79 to 06/30/81

FY 81: -0- (Ann. \$47,708)

Dr. Neal K. Clapp, The University of Tennessee, Oak Ridge National Laboratory,
P.O. Box Y, Oak Ridge, TN 37830

Objectives: Since epidemiological evidences suggest that high fiber diets may protectively modify colon cancer incidences, we are investigating the effect of different kinds of bran (corn, soybean, soft winter wheat, and hard spring wheat) on 1,2-dimethylhydrazine (DMH)-induced colon cancer in Balb/c mice. Whereas some previous experiments have used poorly defined bran and/or fiber sources, we are examining the effects of brans which have been chemically analyzed. Thus, we can compare not only the effects of different fiber sources on colon tumors, but possibly identify critical bran components which cause the observed effects.

Accomplishments: Mice given semisynthetic diets with or without added bran and with or without DMH treatment, have been killed (at 40 weeks after the beginning of DMH treatment) the colon cleared, tumor incidences determined, and tissues processed for histological confirmation and evaluation.

Unexpectedly, each of the bran treated groups given DMH have higher tumor incidences than those mice given a control (no added bran) diet with DMH. Final incidences are control - 13%, soybean - 44% soft winter wheat - 48%, hard spring wheat - 58%, and corn bran - 72%. A group of mice given control diet during DMH treatment and then placed on a soft winter wheat bran diet also had increased tumor incidences (33% vs. 13% for controls). This indicates that bran may act during the promotion phase of tumorigenesis. Tumors/tumor-bearing mouse were 1.2 - 1.3 in mice on the control diet and 1.6 in soybean and the two wheat brans, but 2.2 in mice on corn bran. Another group of mice given DMH was maintained on Purina laboratory chow; a 21% tumor incidence was observed in this group. The consistent finding that mice given bran-supplemented diets had enhanced tumor incidences after DMH treatment may reflect species differences in susceptibility and suggests that results from previous studies which have been primarily conducted in the rat, may not be as general in scope as has been postulated. To date, the only correlation of tumor incidence with the various bran components is with neutral detergent fiber (NDF); this correlation suggests that the higher the NDF in the diet, the higher the tumor incidence after DMH. The possible prognostic value of this relationship is being examined. We have also measured fecal β -glucuronidase levels, and have observed a DMH effect (usually depressing) which persists several weeks after initiation and a bran effect which varies with the different bran sources.

Plan: We anticipate completing the histological evaluation of the colon tumors and the statistical evaluation of the data which will permit correlation of the results with the bran component. We will determine the prognostic value of the fecal β -glucuronidase activity for colon tumor incidence.

Publications:

Clapp, Neal K., London, Jerry F., Henke, Marsha A., and Shock, Teresa L.: Enhancement by Dietary Bran of 1,2-Dimethylhydrazine Colon Carcinogenesis in Male BALB/c Mice. Proc. Amer. Assoc. Cancer Res., 22:114, 1981.

Program Director: Vincent J. Cairolì, Ph.D.

Grant 25516: Reducing Adverse Reactions to Cancer Chemotherapy

From 04/01/79 to 03/31/83

FY 81: \$50,129

Dr. Thomas G. Burish, Vanderbilt University, Department of Psychology,
134 Wesley Hall, Nashville, Tennessee 37240

Objectives: The purpose of this project is to investigate the effectiveness of progressive relaxation and biofeedback in reducing the conditioned anxiety, nausea, and vomiting responses developed by many cancer patients who receive chemotherapy. The project includes clinic investigations with patients who have had previous chemotherapy treatment as well as with those who are awaiting their first chemotherapy treatment, and a retrospective investigation of the possible significance of demographic and psychosocial variables in determining whether a cancer patient will profit from behavioral treatments. At a more general level, this research will contribute to a deeper theoretical understanding of the acquisition of adverse behavioral reactions, and of the methods by which these reactions can be ameliorated.

Accomplishments: During the past year, two studies were completed and a third was begun. The two completed studies involved progressive muscle relaxation training and differed primarily in the subject population sampled: one involved chemotherapy patients receiving short push injections, while the other involved patients receiving longer infusions. Patients in both studies were assigned to one of three conditions: (a) relaxation training; (b) therapist control, in which a therapist was present immediately before and during chemotherapy but did not provide systematic relaxation training; and (c) no treatment control. All patients participated in one pretreatment, three treatment, and two followup sessions. Results indicated that during the treatment sessions, patients in the relaxation training condition reported significantly less anxiety, depression, and nausea, and had significantly lower pulse rates and systolic blood pressures, than patients in either the therapist control or no treatment control condition, who in turn did not differ reliably from each other. Several of these relaxation effects diminished considerably during the followup sessions when relaxation training was no longer administered. These results suggest that therapist-directed relaxation training can be a highly effective procedure for reducing adverse reactions to cancer chemotherapy. However, it appears that additional research is needed to develop more effective procedures for increasing the generalization of the effect to followup (nontreatment) sessions.

The study began during the last year and currently still in progress assesses both the comparative effectiveness of relaxation training, EMG biofeedback training, and skin temperature biofeedback training, and the combined effectiveness of relaxation training plus either type of biofeedback training, in reducing the distress of cancer patients undergoing chemotherapy. Appropriate control groups are also included. Preliminary investigation of the data suggests that relaxation training and/or EMG biofeedback training produce a reliable decrease in several adverse reactions to chemotherapy.

Program Director: Sandra M. Levy, Ph.D.

Plans: Future research will assess the effectiveness of behavioral procedures in reducing conditioned aversive responses to cancer chemotherapy, preventing the development of such responses in new chemotherapy patients, and comparing the effectiveness of behavioral procedures to anti-anxiety/anti-emetic medication. Finally, a retrospective study will be conducted to identify whether psychosocial factors might predict which types of patients will profit from behavioral procedures.

Publications:

Burish, T.G. and Lyles, J.N.: Effectiveness of relaxation training in reducing adverse reactions to cancer chemotherapy. J. Behav. Med. (in press).

From 04/01/80 to 03/31/83

FY 81: \$405,240

Dr. Charles B. Arnold, American Health Foundation, 320 East 43rd Street,
New York, New York 10017

Objectives: This research project is a longitudinal cohort study designed to test the effectiveness of a school-based, teacher-delivered health education curriculum in preventing the development of behaviors in children known or hypothesized to lead to increased risk for cancer. Among the behaviors targeted for intervention are cigarette smoking, alcohol consumption and consumption of a high-fat, low fiber diet. Behavioral outcomes in the intervention schools will be compared to those in comparison schools, in which no cancer-prevention curriculum was implemented.

Accomplishments: The cancer-prevention curriculum was implemented for the first year in the 15 intervention schools among the study cohort of fourth grade children (ages 9 and 10). The curriculum emphasized personal assumption of responsibility for health, appropriate health decision-making processes, explanation of risk-promoting health behaviors, promotion of attitudes conducive to the adoption of healthful behaviors, the relationship of self-esteem to health behaviors, promotion of a habitual diet lower in total and saturated fat and higher in fiber, and the prevention of cigarette smoking and alcohol consumption. Both study (N=1500) and comparison (N=600) cohorts were screened at the onset of the 1980-1981 school year for cognitive, attitudinal, behavioral and biomedical parameters of risk. These data are currently being analyzed. Evaluation will consist of comparing the outcome parameters between study and comparison cohorts, specifically, cancer-prevention related knowledge and attitudes, habitual nutrient consumption, and cigarette smoking and alcohol consumption incidence rates. The Program has achieved high acceptance and favor among children, parents, teachers and school administrators.

Plans: This project will follow the study and comparison cohorts for three years, from fourth through sixth grades (ages 9 through 11). A renewal application will be submitted to permit continuation of the study through junior high school, a time period when poor nutritional habits, cigarette smoking and alcohol consumption become highly prevalent.

Program Director: Andrew F. Hegyeli, D.V.M., Ph.D.

Grant 25523: Project CHOICE--Cancer Prevention is Your Choice

From 4/1/81 to 7/31/81 FY 81: \$236,509 (estimate)
Dr. William B. Hutchinson, Fred Hutchinson Cancer Research Center,
1124 Columbia Street, Seattle, Washington 98104

Objectives: Project CHOICE is a model program to teach school children, grades K-12 in Washington State, about cancer risk reduction and cancer prevention. The curriculum units will be evaluated statewide using a multiple time-series model to measure cognitive and attitudinal changes, as well as information evaluation and decision-making skills and behavioral changes. State curriculum validation and Joint Dissemination Review Panel (JDRP) approval will be sought in conjunction with the program evaluation. Statewide dissemination and implementation of the curriculum units will be aided by, but not contingent on, State validation and JDRP approval.

Accomplishments: Pilot testing of prototype units of cancer education materials for elementary and secondary schools was completed in February 1981. The K-6 curriculum units were pilot tested in the Bethel School District; the Junior High School curriculum was piloted in the Edmonds School District; and the High School curriculum was piloted in the Highline School District. Individual teaching units were developed for each grade K-6, and for the Junior and Senior High School levels. Each of the nine grade units was designed to be taught by the regular classroom teacher; each curriculum unit consists of two weeks of lessons, and includes slide shows, worksheets, situational decision-making problems, group work and discussion questions. Eight broad areas related to cancer risk are included: Host Factors, Drugs--including alcohol and tobacco, Occupational Hazards and Occupational Safety, Environmental Hazards, Stress, Nutrition, Sexual and Reproductive Behavior and Sun Exposure. The units also include an emphasis on individual decision-making skills and on accepting personal responsibility for health and wellness. A Project CHOICE staff person observed each lesson as it was being taught, and teachers and students were interviewed following each lesson. Curriculum revisions are being done in accordance with this initial process evaluation.

Plans: (1) To complete revisions of K-12 curriculum materials; (2) to develop an evaluation plan to serve four purposes: (a) to determine whether the Project CHOICE curriculum changes students' knowledge, attitudes, behaviors, and perceptions relating to cancer, cancer risk reduction and early detection practices; (b) to determine whether documented behavior and knowledge change is a result of Project CHOICE or other external variables; (c) to provide a model for evaluating other cancer curriculums, including instrumentations; (d) to serve as the data base for State curriculum validation and approval by the Joint Dissemination and Review Panel (JDRP); (3) Seek State curriculum validation and JDRP approval; and (4) Implement Project CHOICE curriculum units statewide.

Publications:

Reis, E., "Cancer Prevention Education", Context and Conflict.
Journal, Washington State Association for Supervision and Curriculum
Development, Spring 1980.

Program Director: Arlene R. Barro, Ph.D.

Grant 25554: Clinical Cancer Education Program

From 07/01/79 to 06/30/82 FY 81: \$57,936
Dr. Laurence Elias, Cancer Research and Treatment Center
University of New Mexico School of Medicine, Albuquerque, N.M. 87131

Objectives: The program is designed: (1) to improve the attitudes of students and physicians studying and training at our medical center towards patients with cancer; (2) to increase medical students' basic knowledge of cancer biology and medicine by strengthening courses; (3) to encourage clinical medical students' participation in oncology electives; (4) to improve nursing attitudes and expertise relevant to oncology by developing an oncologic nursing education program.

Accomplishments: (1) A program was established to provide specific instruction and counseling to medical students concerning their interactions with patients with cancer. This includes small class experiences in the first and second years of medical school, videotaped interviews with simulated cancer patients, and administration of standardized instruments to evaluate the impact of this program. The program is also being extended into the third year of medical school with a study investigating role-modeling during the medicine rotation. (2) A cancer biology and medicine block for the second year of medical school was designed and taught to successive cohorts of medical students. This block emphasizes clinical-basic science correlation and multidisciplinary approach to management of cancer patients. The block includes an elective program, which is enthusiastically subscribed to by the students. (3) Students have continued to rotate through the various oncologic specialty rotations. An increased level of interest has been expressed in rotations through radiation oncology. (4) An oncology nursing program has been established which includes increased cancer patient care teaching in the nursing school curriculum, an extensive clinical staff development program, a patient education program, and the organization of several statewide nursing conferences and workshops.

Plans: During the coming year, in addition to continuing the activities described above, we hope to analyze the data from our ongoing studies of students and physicians' attitudes towards cancer, broaden the instructional and counseling activities relevant to this area, and implement more formal evaluation of successive classes' objective knowledge of oncology through review of National Board of Medical Examiners' standardized tests. This information will be used to pinpoint areas needing further attention and to help plan for improvements in subsequent years of the program.

Program Director: Margaret H. Edwards, M.D.

From 07/01/79 to 06/30/82

FY 81: \$67,529

Dr. Beatrice C. Lampkin, Children's Hospital Medical Center
Ebland & Bethesda Avenues, Cincinnati, Ohio 45229

Objectives: The program is designed to improve understanding of childhood cancer by the medical profession, paramedical personnel and the community. The program covers (1) the recognition of childhood cancers, (2) diagnostic approach, (3) multidisciplinary treatment programs, (4) current results of treatment of childhood cancer, and (5) rehabilitation of survivors of childhood cancer.

To enrich the regular curriculum lecture series, tumor board meetings and elective programs are offered to medical students and residents to provide an in-depth understanding of the multidisciplinary management of childhood cancer. Clinical Assistant and Clinical Associate programs are available. Slides, videotapes, and information packages are developed and used in the education of various target audiences.

Accomplishments: (1) A multi-image slide presentation entitled "Childhood Cancer--Today's Crisis, Tomorrow's Challenge" features one local family's struggle to regain some sense of normalcy in their lives following their 7-year old son's diagnosis of leukemia. This has been shown to medical professionals, nurses and nursing students, educators, college students, church groups, patients and families, and other community groups. (2) Videotapes have been made with interviews with parents whose children have died from cancer describing their feelings from diagnosis till death of the child and how they coped after the child's death. These tapes emphasize the importance of psychosocial support to parents by the oncology staff, pediatric housestaff, nurses, medical students and social workers. (3) Information packages on various childhood cancers and available facilities for cancer treatment have been compiled for distribution to educators, nursing students, health professionals, college students, community groups, church members, patients and families, high school students and the media. (4) A summer Clinical Assistant program is offered to 4-6 sophomore students as an early introductory course in clinical oncology, helping them to understand the difference between adult and childhood cancers and the principles of multidisciplinary management of cancer. (5) A clinical Associate program is offered to a pediatric fellow and a pediatric surgical fellow to provide a comprehensive training in pediatric oncology. (6) Dr. Maloney, psychiatrist, is conducting weekly group sessions with nurses in the oncology ward, focusing upon the professional stresses of working with cancer patients and families. (7) The Nursing Committee for Clinical Cancer Education is compiling a manual on chemotherapy and radiotherapy for nurses, housestaff and parents. (8) Monthly educational meetings are given to a parents' group by oncology staff, psychiatrist, radiotherapist and dentist.

Plans: (1) A symposium on "Total Health Care of Cancer in Children" is planned for April 1981 with co-sponsorship from the Cincinnati Pediatric Society. The target audience will be practicing physicians and nurses. The topics will cover ancillary supportive care of a child with cancer such as nutrition, dental care, management of fever and financial and community resources.

Program Director: Margaret H. Edwards, M.D.

(2) A newsletter entitled "Childhood Cancer Communique" will be distributed to physicians and nurses with current cancer news and topics of cancer management. (3) A book on childhood cancer for the lay public will be compiled. (4) A study of late effects on long-term survivors of childhood cancer will be established.

Grant 25570: Community-Based Cancer Nursing Education Program

From 4/1/79 to 3/31/82

FY 81: \$161,145

Dr. Gail Hongladarom, Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, Washington 98104

Objectives: The overall objectives of the Community-based Cancer Nursing Program are to develop a basic cancer nursing continuing education curriculum and to present it to registered nurses in communities throughout the Pacific Northwest and Alaska. An additional objective is to conduct pre- and post-program evaluations of participants to identify change that can be attributed to participation in the program.

Accomplishments: During year 02 the 80-hour curriculum was presented to registered nurses in the following communities:

Anchorage, Alaska
Spokane, Washington
Boise, Idaho
Missoula, Montana
Yakima, Washington
Tacoma, Washington

Even though the nation is currently facing a critical shortage of registered nurses, each program has registered between 20 to 25 participants. In some communities nurses have had to be told the course was filled. Recruitment of program participants was anticipated to be one of the program's most serious potential problems. This has not occurred. Nurses come from hospitals, physician's offices, health departments, home health agencies and hospices. With so many hospitals opening separate oncology units, it seems that additional cancer nursing programs should be developed across the nation to assure that patients receive quality cancer nursing. The accreditation of oncology units should consider the educational preparation of the nurses working in these unique settings.

The program faculty not only teach the two-week cancer nursing curriculum, but also fill many requests from hospitals, institutions and interested cancer groups to talk on a variety of topics: screening and detection, chemotherapy, pain management, management of treatment side effects and terminal care in the home, and bereavement counseling. This program has increased the visibility of the role of cancer nurses in the quality management of cancer patients and their families. The program faculty and staff have also increased the understanding of the role of the comprehensive cancer center in the Northwest/Alaska region. Several papers for publication in professional journals are in preparation.

Plans: Goals for the coming year include planning with seven additional communities in the service area of the Fred Hutchinson Cancer Research Center to lay the groundwork for the implementation of the two-week course. Another goal of the project is to complete the unique evaluation component and draft a

Program Director: Graceann Ehlke, R.N., M.N.

report of the findings. Also a goal for the upcoming funding period is to finalize the format of the curriculum and supplemental materials so this can be shared with other cancer centers and institutions which have the appropriate personnel and institutional support to sponsor this type of cancer nursing educational program. Re-visits to some communities in which the program has already been presented for update and refresher sessions is being planned. An important part of this final year is that the mechanism for continuation of this continuing education project be worked out with either the Fred Hutchinson Cancer Research Center or the community college system of the State of Washington.

From: 04/01/79 to 03/31/82

FY 81: \$122,502

Dr. Robert J. Hay, Cell Culture Department, American Type Culture Collection,
12301 Parklawn Drive, Rockville, MD 20852

Objectives: The objectives of this program are to develop and to otherwise obtain, characterize, expand, bank and distribute cell lines of use for studies on cancer of the large bowel. These include tissues of human and laboratory animal origins. These efforts will ultimately provide well characterized cell lines for the entire scientific community. Reference material will thus be made available over the long-term such that comparative studies will be possible both within a given laboratory and among different laboratories throughout the world. In addition, information should be generated concerning the properties of colon cell lines in common use and the requirements for isolation and propagation of colonic cells (normal and tumorigenic) in vitro.

Accomplishments: A committee organized early in the program, reviews literature describing properties of lines from human and murine colorectal tumors and examines credentials of lines banked before release to the general scientific community. One human colon line purported to be epithelial and normal, twenty-five cell lines from human colorectal tumors, two skin fibroblast strains from individuals predisposed to adenomatosis of the colon, a chemically induced tumor of the mouse and three normal mouse intestinal epithelial lines have been received. In addition, three fibroblast-like strains from colon tissue of presumptive normal humans of differing ages have been characterized for distribution. The species of each line has been verified by isoenzymology and each has been tested for the presence of bacterial, fungal, viral, and protozoan contaminants. Seed and distribution stocks have been prepared on suitable lines. Progeny from these stocks have been or are being characterized further with regard to karyology, isoenzymology, tumorigenicity, growth properties, antigenic markers, and ultrastructure as appropriate. Nineteen such reference lines are currently available. Isolation and cell line development has been conducted on normal colonic tissue from humans and African green monkeys, and on human colon, rectal, and cecal tumors. Epithelial-like populations have been obtained from both source species. Success in isolating propagable fibroblasts from normal source material has been high, but the doubling potential of these populations is considerably lower than that observed with fibroblasts from skin and lung.

Plans: Cell lines from individuals in families predisposed to bowel cancer will be submitted in the near future. In addition we hope to obtain recently isolated human colon tumor variant lines, new colonic epithelial lines from rat and mouse, and transplantable colorectal tumors of human and other animal origins. The development of hybridoma cell lines which produce monoclonal antibodies to antigenic determinants on both normal and malignant intestinal cells has been reported recently. We hope to add many of these to the bank. Characterizations including additional electrophoretic analyses and determinations of surface marker antigens will be extended for all banked colorectal lines.

Publications:

Hay, R.J.: Collection of Human Tissues for Use in Cell Culture Research. TCA Manual, 5:1099-1106, 1979.

Program Director: Vincent J. Cairoli, Ph.D.

Grant 25650: A New Method Using Omentum to Reconstruct Deformities

From 08/01/79 to 07/31/81

FY 81: 0 (Ann. \$102,771)

Dr. Melvin Spira, Baylor College of Medicine, 1200 Moursund Avenue,
Houston, Texas 77030

Objectives: To develop a method for vascularizing skin, muscle cartilage and/or bone with greater omentum to obtain an island flap. In the second year of this study, the following goals were set: First, to determine the optimum time between attachment of the omentum to the composite flap and transfer of this vascularized flap. Second, to improve the method for attachment of the omentum pedicle to bone and to develop a technique for transfer which will continue viability of the omental bone pedicles in their recipient sites. Third, to compare the effectiveness of tibial, costal and iliac osteocutaneous flaps at different recipient sites in an effort to determine the most suitable bone to be employed in clinical reconstructive surgery.

Accomplishments: In twenty-one pigs omentum was exteriorized, placed under abdominal skin which was, at intervals between 10 to 35 days, raised completely on the omental pedicle and its vascularity and studied. In vivo studies included fluorescein dye and radioactive Xenon and at the time of sacrifice, microangiography. Vascularization of the island pedicle skin flaps with omentum was successful in all groups, but with two weeks of omentum augmented vascularity the operation was technically the least difficult. Transfer of the pedicle, employing microvascular anastomosis, should be performed immediately after mobilization of the pedicle on the omentum, as any delay resulted in a tendency to flap thickening up to four times its original measurement. Next, employing twenty-eight pigs in forty-nine experiments, composite osteocutaneous island flaps have been developed, using the tibial bone, costal bone and iliac crest bone, either enveloped in a skin omental tube or wrapped with omentum. Vascularization of costal and iliac bone grafts with omentum was achieved as early as fourteen days and confirmed by fluorescein dye, tetracycline labeling, radioactive isotope and microangiographic studies in each experiment. In so doing it was possible to fully preserve bone integrity and its continued vascularization prior to and after transfer. Isotope activity reached peak levels at twenty-one to forty-two days, leveled off and then gradually decreased over the one year period of study. Thus, these findings suggest that we can transfer the secondary island osteocutaneous flap as early as twenty-one days and shouldn't wait more than three months for the distal transfer clinically the reconstructive effort.

Plans: We will maintain the animals in which bone graft reconstruction of the mandible were performed for at least a year to check for late resorption. Comparison of the effectiveness of the three types of osteocutaneous flaps (tibial, costal and iliac) with different recipient sites will continue to be made using the parameters described above.

Publications:

O. Onur Erol, M.D. and Melvin Spira, M.D.: Secondary Musculocutaneous Flap: An Experimental Study, Plast. and Reconstr. Surg., Vol. 65, No. 3, March 1980.

Program Director: Lawrence D. Burke

O. Onur Erol, M.D. and Melvin Spria, M.D.: New Capillary Bed Formation with a Surgically Constructed Arteriovenous Fistula, Plast. and Reconstr. Surg., Vol. 66, No. 1, July 1980.

O. Onur Erol, M.D., Melvin Spira, M.D., D.D.S. and Barnet Levy, D.D.S.: Microangiography: A Detailed Technique of Perfusion, Journal of Surg. Research, Vol. 29, No. 5, November 1980.

Grant CA 25657: Ohio Statewide Cancer Control Support and Development Grant

From 09/01/79 to 06/30/82

FY 81: \$174,000 est.

Dr. C. J. Cavalaris, Comprehensive Cancer Center, The Ohio State University
101A Hamilton Hall, 1645 Neil Avenue, Columbus, Ohio 43210

Objectives: The Comprehensive Cancer Center will assist in the development of a statewide Consortium for Cancer Control in Ohio that will annually assess the needs, assess resources, and prioritize needed programs in each of ten regions in Ohio. Ten regional cancer councils, bases upon HSA regions, will be developed based upon the regional assessments. Additionally, the Center will assist in developing two regional cancer resource centers and through a mini-grant process encourage community hospitals to develop cancer related programs.

Accomplishments: The statewide organization, the Cancer Control Consortium of Ohio, has ratified a Code of Regulations and has been incorporated. Twenty-six different "profiles" of Cancer Control resources statewide have been distributed to regional councils for their use in prioritizing needs; 15 sub-region profiles; 1 state profile. An interactive computer system--HOSWRITE--has been developed to provide customized data displays which "profile" individual hospitals. The system offers flexibility to local-level Cancer Control Personnel, hospital representatives, who need to formulate query "problems" unique to their respective settings. Two cancer resource centers have been established, one at Wright State University in Dayton, Ohio and the other in Athens, Ohio at the Consortium for Health Education in Appalachia Ohio, Inc. Both of these resource centers have cancer coordinators that have been active in developing cancer related activities in their respective regions. Over 100 public and professional education programs have been presented. A third resource center has been established in northeast Ohio (three regions) with a cancer coordinator to develop multi-regional cooperatives, educational programs, and community hospital networks for cancer related activities in this large area. A statewide oncology nurse network is being developed to identify regional needs for cancer nursing education and training, facilitate communication and coordination and to provide education program for nurses. A community hospital planning grant committee has funded nine community hospital mini-grants to assist rural community hospitals in upgrading cancer programs.

Plans: The resource inventories and hospital surveys will be updated and the development of regional needs assessments and prioritized interventions established. The Consortium will evaluate the regional plans and develop a statewide plan with priorities for Cancer Control Activities in Ohio based upon the regional plans. Full development of an oncology nurse curriculum, an oncology nurse network into all regions, and the delineation of priority educational needs in each region will be accomplished. Community hospital cancer programs and cancer patient care within rural communities will be upgraded.

Program Director: Carlos E. Caban, Ph.D.

Publications:

Cavalaris, C.J., and Miller, Patricia L.: A Statewide Organization for Cancer Control. In Meetlin, Curtis (Ed.): Progress in Cancer Control 1980. New York, Alan R. Liss, Inc. IN PRESS

Pamphlet, Cancer Control Consortium of Ohio.

Grant 25662: In Vitro Assay for Increased Risk for Pancreatic Cancer

From 09/20/79 to 08/31/81

FY 81: 0 (Ann. \$33,631)

Dr. Betty S. Danes, M.D., Ph.D., Laboratory for Cell Biology, Department of Medicine, Cornell University Medical College, New York, New York 10021

Objectives: The aims of this research are to (1) identify biological properties in monolayer skin cultures which make recognition of increased genetic risk for pancreatic cancer possible prior to clinical expression, (2) increase our understanding of the role of genetics in pancreatic cancer, and (3) give a basis for counselling of genetic risk and cancer surveillance.

Dermal monolayer cultures derived from families with pancreatic cancer will be assayed for four biological properties (morphology, growth kinetics, mitoses and transformation); each assay is considered to reflect a different biological change that disrupts the regulation of in vitro growth. A change in any one, appearing in all clinically affecteds and showing vertical transmission within a family, would be considered to be due to a mutation which would indicate increased genetic risk for pancreatic cancer due to cancer prone gene/s in their genome.

Accomplishments: Genetic risk for pancreatic cancer in this in vitro research has been divided into four groups on the basis of family pedigrees and clinical histories: (I) pancreatic cancer in association with other solid tumors (Cancer Family Syndrome), (II) pancreatic cancer in association with hereditary pancreatitis, (III) pancreatic cancer in consecutive generations without any other recurrent solid tumors, and (IV) single cases of pancreatic cancer without other clinically affecteds within a family/kindred.

Kindreds with members with such pancreatic cancer in consecutive generations have been identified and detailed pedigrees established. Vertical transmission of pancreatic cancer has been considered evidence of a genetic component of pancreatic cancer within such families. Dermal (mixed fibroblast-epithelioid) cultures were established and assayed for occurrence of in vitro tetraploidy and growth kinetics associated with transformation.

These in vitro studies have shown altered in vitro biological properties which distinguish those affecteds studied in the four groups from unaffected controls. Increased in vitro tetraploidy has been observed in cultures derived from clinically affecteds and some family members at risk in groups I and III; growth kinetics in cultures from affecteds in group IV have been altered as compared to those from normals considered not to be at increased risk for pancreatic or any other solid tumor.

Plans: On the basis of the above research, assays to be carried out on families in groups I-IV fall into three categories: (1) cytogenetic studies (evaluation of in vitro tetraploidy and cytogenetic analyses using appropriate banding techniques); (2) growth kinetics (growth curves to determine generation time, influence of cell density on growth, saturation density); (3) spontaneous and induced (in response to carcinogens) transformation assayed by selection of anchorageindependent clones, one of the properties associated with transformation.

Program Director: William E. Straile, Ph.D.

From: 03/01/79 to 02/28/82

FY 81: \$54,296

Dr. Maryce M. Jacobs, The Eppler Institute for Research in Cancer, University of Nebraska, 42nd and Dewey Avenue, Omaha, NB 68105

Objectives: The overall objective is to study the role of Selenium (Se) in inhibiting and/or reversing 1,2-dimethylhydrazine (DMH)-induced carcinogenesis in Sprague Dawley (SD) rats. To insure use of subtoxic levels of Se in the carcinogenesis studies, we will evaluate the acute and chronic toxicity of Se as Na_2SeO_3 . The mechanism(s) by which Se reduces tumor incidence and slows tumor growth is being investigated. The findings may have potential preventive and therapeutic benefit in colon cancer.

Accomplishments: The biochemical and clinical effects of selenium (Na_2SeO_3) on DMH-induced colon carcinogenesis in SD rats have been evaluated. Se supplement to the drinking water (4 ppm) was provided before, during and after 20 weekly injections of 20 mg DMH/kg body weight. Provision of Se during DMH treatment reduced the colon tumor incidence from 63% in DMH-only treated controls to 36% at 41 weeks of age. Administration of Se for 10 weeks preceding DMH treatment, (a), or before and during DMH treatment, (b), reduced the colon tumor incidence to 39% (a) and 43% (b), respectively at 41 weeks of age. At 20 weeks following the last DMH injection all groups receiving DMH had a mean colon tumor incidence of 90%. Early supplements of Se reduced the colon tumor incidence. Later supplements of Se slowed tumor growth. The white blood count (WBC) increased with increased incidence of colon tumors. Selenium supplementation after DMH treatment returned the WBC closer to the normal range. The increased growth of the colon tumors and the appearance of tumors at extra colonic sites were associated with a marked decline in hemoglobin. The serum acid phosphatase activity decreased with Se supplementation and the colonic β -glucuronidase activity increased as the increased incidence and growth of colon tumors were observed. Se increased 2-fold in liver over the untreated control while glutathione peroxidase (GSHPx) decreased in DMH-Se treated groups. With increased tumor burden and increased time after DMH treatment the alkaline phosphatase and serum glutamate-oxalacetate transaminase levels increased. These increases were greater in Se-supplemented groups than in DMH-only controls. Prolonged supplementation with 4 ppm Se alone caused no detectable toxicity as indicated by survival, body weight, pathology, tissue and blood analyses.

Plans: Studies on the clinical and biochemical evaluation of the effects of Se on DMH-induced colon carcinogenesis using a lower dose of DMH and fewer injections are planned. The relationship between colonic β -glucuronidase, GSHPx and sialic acid, and microscopic pathology in DMH-Se treated animals will be evaluated.

Publications:

Jacobs, M.M. and Forst, C.: Toxicological Effects of Sodium Selenite in Sprague Dawley Rats. J. Toxicol. Environ. Hlth., in press, 1981.

Jacobs, M.M. and Griffin, A.C.: Trace Elements and Metals as Anticarcinogens. In Inhibition of Tumor Induction and Development, M.S. Zedeck and M. Lipkin, Eds. 233 Spring St., New York, NY, Plenum Publishing Corp., Chapter 6, 1981: pp. 169-188.

Program Director: Vincent J. Cairoli, Ph.D.

Grant 25759: Phase II Chemotherapy Studies and Pancreatic Cancer

From 07/01/81 to 06/30/83

FY 81: \$169.00

Frederick, P. Smith, M.D., Georgetown University Hospital, Department of Medicine, Washington, D.C. 20007

Objectives: The majority of patients who present with pancreatic cancer have inoperable disease and consequently the mortality rate for this malignancy has been close to 100 percent. If an impact of survival is to be made, investigations in non-operative management of pancreatic cancer will need to be actively pursued. We have continued studies of combinations of known active single agents in inoperable pancreatic malignancies. The purpose of these investigations is to try to improve the response rate and duration seen in pancreatic cancer by building upon known active agents or combinations. We expect to complete three separate studies under this grant; the evaluation of combination of 5-fluorouracil, adriamycin, mitomycin-C and chlorozotocin in advanced measurable pancreatic cancer, evaluation of 5-fluorouracil, adriamycin and cis-platinum in advanced measurable pancreatic cancer, and the evaluation of 5-fluorouracil, adriamycin and mitomycin-C in the management of locally advanced pancreatic cancer. By identifying active combination regimens in these pilot trials, we expect to promote their study in group-wide Phase III study.

Accomplishments: The first Phase II Study completed under the auspices of this grant has been the trial of the combination of 5-fluorouracil, adriamycin, mitomycin-C and chlorozotocin. During an earlier Phase II trial of the first three drugs, we had detected a 37 percent response rate in 29 patients with advanced measurable disease, with a median duration of response of 10 months. The intent of this program was to try to improve the response and duration by adding the new, relatively myelosparing chloroethyl nitrosourea, chlorozotocin. Twenty-three consecutive patients with metastatic measurable pancreatic carcinoma were treated with the FAM chlorozotocin regimen. The treatment was found to be well tolerated with mild nausea and vomiting and moderate myelosuppression as its major toxicity. Three of 23 (13 percent) patients treated with this regimen responded. An additional five had disease stabilization. The median survival for all patients is 6.4 months with a range of 1 to 15 months. The partial response rate with this regimen was not as good as that observed with FAM and the trial was closed in May of 1980. With the conclusion of FAM chlorozotocin, we embarked upon the five fluorouracil, adriamycin in combination with cis-diamminedichloroplatinum. Eighteen consecutive patients with histologically documented pancreatic cancer have been treated with FAP: three patients have obtained objective tumor regression, and two additional patients have achieved disease stabilization. Gastrointestinal toxicity in the form of acute nausea and vomiting during cis-platinum therapy was a predominant side-effect noted. Myelosuppression has been mild. It is too early to draw any general conclusions on the activity of FAP in pancreatic cancer. It is expected that at least five more patients will be accrued on this study by the end of this grant. The third trial of FAM in locally advanced pancreatic cancer was stimulated by the awareness that combined modality therapy of 5-fluorouracil with radiation represented a palliative form of therapy with a projected survival at two years of 10 percent or less. With the demonstrated efficacy of FAM in metastatic pancreatic cancer, it appeared warranted to test this regimen

Program Director: William E. Straile, Ph.D.

in earlier stages of disease. Sixteen consecutive patients with disease confined to a radiation treatment portal were treated with the FAM combination. Preliminary results suggest that the treatment is quite well tolerated, the median survival for the present treatment population is an excess of seven months which appears to be at least as good as that achieved with 6,000 rads alone. It is anticipated that an additional 5 or 10 patients will be accrued on this study by September, 1981.

Plans: We propose to continue our Phase II investigations in advanced pancreatic cancer. After concluding the 5-FU, adriamycin and cisplatin study, we would propose the study adding the newly found active hexamethylmelamine to FAM to test its contribution to the treatment of pancreatic cancer. We would also propose an innovative combined modality approach using a combination of chemotherapy with radiation in a sandwich technique for locally advanced pancreatic carcinoma. These innovative programs have been presented to group meetings and similar studies are being considered.

Publications:

Smith, F.P. and Schein, P.S.: Chemotherapy of pancreatic cancer. In Seminars and Oncology, 6:368-377, 1979.

Zimmerman, S.E., Smith, F.P., and Schein, P.S.: Chemotherapy of pancreatic cancer. Cancer 47:1724-1728, 1981.

Grant 25760: Prostate Steroid Receptors by Fluorescence Microscopy

From 04/01/79 to 03/31/81

FY 81: %0 (Ann. \$73,012)

Dr. Louis P. Pertschuk, Department of Pathology, Downstate Medical Center, SUNY, 450 Clarkson Avenue, Brooklyn, New York 11203

Objectives: Prostate carcinoma is known to be a hormone-responsive tumor in the majority of cases, but not in all. Biochemical steroid hormone assays for estrogen and androgen are notoriously difficult to perform and interpret. The objective of this project is to develop a histochemical assay for estrogen and androgen binding in prostate cancer, and to determine its validity by comparison of results with those of conventional biochemical androgen receptor assay, and where possible with the clinical response of prostatic carcinoma to various hormonal therapies. It is hoped that performance of histochemical studies will enable clinicians to select the form of therapy most likely to prove beneficial and will be capable of performance at the community hospital level.

Accomplishments: Androgen binding assay results by biochemical methods showed significant correlation with the histochemical assay in 103 cases as to positivity and negativity, amount of steroid bound and the intracellular location of binding ($< .01$). In 20 cases where response to hormonal treatment could be assessed, histochemistry correlated with response or to lack of response in 19. The number of cases available for correlation should double by the end of the grant period.

Plans: It is planned to continue histochemical steroid binding assays emphasizing correlations with clinical response in patients with advanced disease until a statistically significant number of patients have been studied. In addition, new techniques designed to detect steroid hormone binding sites with other, entirely different histochemical probes are under development and will be similarly correlated.

Publications:

Pertschuk L.P., Rosenthal H.E. Macchia, R.J., Eisenberg, K.B., Feldman, J.G., Wax, S.H., Kim D.S., Whitmore, W.F., Jr., Abrahams, J.I., Gaetjens, E., Wise, G.J., Herr, H.W., Karr, J.P., Murphy, G.P., Sandberg, A.A.: Correlation of Histochemical and Biochemical Analyses of Androgen Binding in Prostatic Cancer: Relation to Therapeutic Response. Cancer, (In press).

Pertschuk, L.P., Tobin E.H., Brigati, D.J., Gaetjens, E.: Morphologic Assay of Steroid Hormone Receptors in Human Neoplasia. In Pathology Annual. 1980, pp. 143-180.

Pertschuk, L.P., Tobin E.H., Gaetjens, E., Brigati, D.J., Carter, A.C., Degenshein, G.A., Kim D.S., Bloom, N.D.: Histochemical Assay of Steroid Hormone Receptors. In Perspectives in Steroid Receptor Research. F. Bresciani, Ed., Raven Press, New York, 1980. pp. 299-309.

Program Director: Andrew Chiarodo, Ph.D.

Pertschuk, L.P., Tobin E.H., Tanapat P., Gaetjens, E., Carter, A.C., Bloom, N.D., Macchia, R.J., Eisenberg, K.B.: Histochemical Analyses of Steroid Hormone Receptors in Breast and Prostate Carcinoma. J. Histochem. Cytochem. 28:799-810, 1980.

Pertschuk L.P., Gaetjens, E., Eisenberg, K.B.: Steroid Hormone Receptor Proteins. Histochemical Markers of Potential Hormone Dependence. In, Methods and Achievements in Experimental Pathology. G. Jasmin, M. Cantin, Eds. S. Karger, Basel, (In press).

Pertschuk, L.P., Carvounis, E.E., Tobin, E.H., Gaetjens, E.: Renal Glomerular Steroid Hormone Binding. Detection by Fluorescence Microscopy. J. Steroid Biochem. 13:1115-1120, 1980.

Pertschuk, L.P., Di Maio, M.F.A.C., Gaetjens, E.: Histochemical Demonstration of Steroid Hormone Binding Sites in the Lung. J. Steroid Biochem. 13:1121-1124, 1980.

Grant 25792: Immunologic Characterization of the Copenhagen Rat Prostatic Adenocarcinoma (R3327)

From 09/30/78 to 08/31/81

FY 81: \$0 (Ann. \$57,642)

Dr. William J. Catalona, Department of Surgery/Urology, Washington University School of Medicine at the Jewish Hospital of St. Louis, 216 South Kingshighway, Saint Louis, Missouri, 63110

OBJECTIVES: The primary objective of this project is to examine immunologic escape mechanisms operative in prostatic cancer, using an animal tumor model. We sought first to determine whether the R3327 tumor is immunogenic in syngeneic hosts by performing classic transplantation resistance experiments and experiments attempting to adoptively transfer resistance with immune lymphocytes. In Vivo results were to be correlated with in vitro assays that ultimately could be applied to humans. The in vitro were: (1) cytotoxicity, (2) mixed lymphocyte-tumor cell interactions, and (3) leukocyte adherence inhibition. Effector cells were to be fractionated to determine the subpopulations responsible for relevant functions. The development of host immunity was to be monitored during tumor growth and the effects of therapeutic manipulations on these phenomena were to be examined.

ACCOMPLISHMENTS: We have performed eight immunogenicity experiments: three with small (2g) immunizing tumors, two with medium-sized (13g) tumors and three with large (25g) tumors. Neither small nor large tumors conferred transplantation resistance, but significant resistance was observed in one experiment with medium-sized tumors and results suggestive of resistance were observed in the other.

Mixed lymphocyte-tumor cell assays revealed that lymphocytes from animals bearing small tumors did not exhibit proliferative responses when co-cultured with tumor cells, but lymphocytes from animals with medium or large tumors did. In vitro cytotoxicity assays have been unsuccessful because of high spontaneous release of isotopes from our two cell lines of the R3327 tumor. To date we have been unable to demonstrate positive leukocyte adherence inhibition responses in tumor-bearing animals.

We also have examined nonspecific immune responses in the R3327 tumor. Injections of the macrophage-toxic agents carrageenan and silica significantly enhanced tumor growth.

Plans: Currently we have three immunogenicity studies with medium-sized tumors in progress. These should provide more evidence about the development of immunity in this tumor model. We plan to pursue our positive results in the mixed-lymphocyte tumor cell interaction and to perform methodologic studies using other isotopes to label target cells for cytotoxicity assays. We also plan further methodologic studies with the leukocyte adherence inhibition assay. We intend to examine relevant effector mechanisms with fractionated cell subpopulations, and examine how they might be modulated.

Publications: Catalona, W.J., T.L. Ratliff and R.E. McCool: Immunology of Prostate Cancer. Advances in Medical Oncology, Research and Education, 11:341 Pergamon Press, Inc., Publ. London. 1979.

Program Director: Andrew Chiarodo, Ph.D.

Ratliff, T.L., R.E. McCool and W.J. Catalona: Antibodydependent and Spontaneous Lympholysis in Urologic Cancer Patients. BRIT. J. CANCER 39:667, 1979. (Data includes prostate cancer patients).

Catalona, W.J., T.L. Ratliff and R.E. McCool: Concanavalin A-Inducible Suppressor Cells in Regional Lymph Nodes of Cancer Patients. CANCER RES. 39:4372, 1979. (Data includes prostate cancer patients).

Catalona, W.J., T.L. Ratliff and R.E. McCool: Characterization of Cell-Mediated Cytolytic Mechanisms Against Human Transitional Cell Carcinoma Line, 253J. IMMUNOLOGY 39:1119, 1980. (The methodology used in this study will be applied to characterization of cytotoxic effector cells for R3327 cell lines).

Catalona, W.J.: Immunobiology of Carcinoma of the Prostate. INVEST. UROLOGY 17:373, 1980.

Catalona, W.J., T.L. Ratliff and R.E. McCool: Con A-Activated Suppressor Cell Activity in Peripheral Blood Lymphocytes of Urologic Cancer Patients. J. NATL. CANCER INST. 65:553, 1980. (Data includes prostate cancer patients).

Catalona, W.J., T.L. Ratliff and R.E. McCool: Characterization of Interferon Induced in Human Lymphocytes by Staphylococcal Protein A. SURG. FORUM XXXI:591, 1980. (Data are relevant to future plans for modulating the immune response).

Ratliff, T.L., R.E. McCool and W.J. Catalona: Interferon Induction and Augmentation of Natural Killer Activity by Staphylococcus Protein A. CELL. IMMUNOL. 57:1, 1981. (Data are relevant to future studies on immune modulation).

Catalona, W.J., T.L. Ratliff and R.E. McCool: Role of Antibody in Cytotoxicity by Lymphocytes Armed Against 253J Bladder Cancer Line. INT. ARCH. ALLERGY AND APPL. IMMUNOL., 1980. (In Press) (Development of methodology relevant to present studies).

Catalona, W.J., T.L. Ratliff and R.E. McCool: Interferon induced by S. Aureus Protein A Augments Natural Killing and Antibody-Dependent cmL. NATURE, 1981. (In press). (Relevant to future studies on immune modulation).

Catalona, W.J., T.L. Ratliff and R.E. McCool. 1980. Immunology of Genitourinary tumors. In Genitourinary Malignancy Vol. I. (Editor, F. Paulson, M.D.). Plenum Press Publ. Co. (In Press).

Catalona, W.J. and R.E. McCool. 1980. Immunotherapy of Cancer. In Recent Advances in Urologic Cancer. (Editor, N. Javadpour). Williams and Wilkins Publ. Co. (In Press).

Grant CA 25878: Absorption of Chaemical Carcinogens in Colon

From: 07/01/79 to 06/30/82

FY 81: \$52,533 (est.)

Dr. Richard C. Rose, The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, PA 17033

Objectives: The project objective is to increase our understanding of intestinal absorption of chemical carcinogens. The significance of this work is that it may help explain the known promoting effect of fecal bile acids on carcinogenesis in animals.

Accomplishments: The specific effects of bile acids as cocarcinogens have been investigated. Absorption of [¹⁴C]-dimethylbenz(a)anthracene (DMBA), [¹⁴C]-dimethylhydrazine (DMH), and [³H]-inulin from loops of rat and guinea pig colon was determined. In each animal absorption of one carcinogen and inulin was studied in one control loop and in an experimental loop containing either deoxycholic acid (DOC) or chenodeoxycholic acid (CDOC). The results indicate that DMH leaves the intestinal lumen more rapidly than DMBA, particularly in the guinea pig. DOC has a more pronounced effect on increasing loss of carcinogen from the intestinal lumen than does CDOC. This role of bile acids is consistent with their known effect of increasing intestinal permeability. Less carcinogen remains in the colonic mucosa when DOC is present in the intestinal lumen. Although DMH is absorbed more rapidly from the intestinal lumen of guinea pigs than from rats, the latter species accumulates more of the carcinogen in the intestinal mucosa and liver.

Plans: We plan to investigate in detail the effects of fatty acids on the transport of carcinogens across colon and into colonic mucosal cells.

Publications: None.

Program Director: Vincent J. Cairoli, Ph.D.

From: 05/01/79 to 04/30/82

FY 81: \$35,433

Dr. Frank E. Jones, The Medical College of Wisconsin, 8700 West Wisconsin Avenue,
Milwaukee, WI 53226

Objectives: The purpose of this study is to demonstrate the efficacy of two anti-oxidants, ascorbic acid (AA) and butylated hydroxyanisole (BHA), given concurrently as single agents and in combination with each other in chemoprevention of 1,2-dimethylhydrazine (DMH)-induced large bowel cancer in CF¹ mice. The effects of oral (systemic) administration versus rectal (local) administration are to be contrasted.

Accomplishments: We have observed that AA in the midrange dosage used in this experiment (100-200 mg/kg/day) demonstrates a marginal chemopreventive effect. Greater and lesser dosages of AA demonstrate no effect on large bowel cancer incidence. BHA shows a significant inhibitory effect against DMH-induced large bowel cancer. Increasing the dosage of BHA did not increase the preventive effect. AA and BHA given together orally produces an additive effect. Rectal injection of AA, BHA, or the combination, shows no preventive effect. Indeed, rectal administration produces a significant increase in anal-rectal tumors not seen with oral antioxidants or in controls. Animals receiving oral antioxidants had a higher incidence of liver tumors than did DMH-treated controls.

Plans: The above observations will be confirmed. In addition, the colon carcinogens azoxymethane (AOM) and methylazoxymethanol (MAM), metabolic products of DMH, will be used to see if bypassing metabolic steps alters the effect of the antioxidants.

Publications: None.

Program Director: Vincent J. Cairoli, Ph.D.

Grant 25903: Epidemiology of Urothelial Cancer in Hawaii

From 09/1/79 - 11/30/82

FY 81: \$0 (Ann. \$64,813)

Dr. A. Nomura, Cancer Center of Hawaii, Honolulu, Hawaii

Objectives: This study is investigating the association of urothelial cancer with coffee, cigarettes, artificial sweeteners, hair dye, occupation, vitamin A and vitamin C in two ethnically-distinct groups which have different levels of risk for this disease (high risk for Caucasians and intermediate risk for Japanese). An attempt is being made to identify all initially-diagnosed cases on the Hawaiian island of Oahu during the period of the study. For each case, two controls from the general population matched by sex, race, and age within three years, are identified and interviewed. The questionnaire and format of the study is similar in design to the case-control study conducted by the Harvard School of Public Health in three different populations (including the low risk Japanese in Nagoya, Japan). By this arrangement, we will be able to compare the findings between the Japanese in Hawaii and Nagoya, as well as between the Caucasians and Japanese in Hawaii to identify factors which may contribute to the difference in risk between the respective groups.

Accomplishments: The study began September, 1979. As of February 28, 1981, 77 cases and 130 controls have been interviewed in the study. We plan to continue identifying and interviewing additional cases and suitable controls for the study.

Plans: After the interviews have been completed in this three-year study, detailed analysis will be done in accordance with the objectives of the study.

Program Director: William E. Straile, Ph.D.

From 06/01/79 - 05/31/82

FY 81: 104,997

Dr. J.B. Vaught, Michigan Cancer Foundation, Detroit, Michigan

Objectives: The abuse of phenacetin-containing analgesics leads to urinary tract tumors in humans. A variety of tumors occur when phenacetin is fed to experimental animals, including bladder tumors in male Sprague-Dawley rats (Isaks et al., Gann, 70: 29-36, 1979). This project concerns the role of metabolic activation in the toxicity and carcinogenicity of phenacetin. Emphasis has been placed on the N-hydroxylation pathway and on the further activation of N-hydroxy-phenacetin. A combination of in vivo and in vitro studies is being used to approach this problem. These include studies using rat liver subcellular fractions, rat liver and bladder cells, as well as an in vivo carcinogenicity study. These studies, described in detail below, have shown that N-hydroxy-phenacetin can be activated to nucleic acid binding metabolites by several pathways. In addition, at the cellular level, N-hydroxy-phenacetin induced unscheduled DNA synthesis in both liver and bladder cells. Since N-hydroxy-phenacetin is a rat liver carcinogen, and phenacetin is a bladder carcinogen, in humans as well as rats, these studies may be important in the elucidation of the mechanisms involved in the induction of tumors by phenacetin and its derivatives. The analysis of data from the carcinogenicity study should provide additional insight into this problem.

Accomplishments: Our initial approach to a study of the metabolic activation of N-hydroxyphenacetin was to perform in vitro experiments using rat liver cytosol or microsomes as sources of activating enzymes, and tRNA as a trapping agent. Radiolabeled N-hydroxy-phenacetin and other phenacetin derivatives, synthesized in our laboratories, served as substrates. In the presence of rat liver microsomes, the binding of [³H-ring]-N-hydroxy-phenacetin to tRNA was increased 3-fold over that of controls. In double-label experiments, the ¹⁴C-acetyl group was lost. The microsome-catalyzed binding was inhibited 90% by paraoxon (diethyl-p-nitrophenylphosphate), a deacetylase inhibitor. p-Nitroso-phenetole, a deacetylated derivative of N-hydroxy-phenacetin, bound to tRNA without enzymatic activation. Studies with liver deacylase, purified from guinea pig, also indicated that the microsomal activation of N-hydroxy-phenacetin was mediated by deacetylation. Binding to tRNA was also catalyzed by rat liver 105,000 x g supernatant. This activity was further purified by ion-exchange chromatography and showed the characteristics of N,O-acetyltransferase. The tRNA adduct produced by this reaction did not retain the acetyl group, a characteristic of acyltransferase-catalyzed reactions with other arylhydroxamic acids. In addition, binding due to activation by the purified enzyme was not paraoxon-inhibitable. Another cytosolic enzyme, sulfotransferase, is also known to be involved in the metabolism of arylhydroxamic acids. We found the cytosol-activated binding of N-hydroxy-phenacetin to be increased 6-fold in the presence of a sulfate-generating system. This reaction proceeded with the retention of the acetyl group, indicating the involvement of a different intermediate than the other reactions described above.

Program Director: William E. Straile, Ph.D.

As an additional approach, cells have been isolated from rat liver and bladder for use in studies of phenacetin metabolism. N-Hydroxy-phenacetin, but not phenacetin, was found to bind to RNA in primary liver cells. In preliminary experiments, unscheduled DNA synthesis has been detected autoradiographically in cultures of liver or bladder cells treated with N-hydroxy-phenacetin.

A carcinogenicity study in Sprague-Dawley-derived rats is underway and will be completed this year. The objectives of this experiment are (i) to confirm previous carcinogenicity data for phenacetin fed to Sprague-Dawley rats, (ii) to determine if saccharin is a bladder tumor promotor for phenacetin carcinogenesis, and (iii) to analyze the effect of feeding ethoxy-deuterated phenacetin as an initiator, since this compound is more slowly deethylated than phenacetin.

Plans: During the coming year, additional nucleic acid binding and metabolism studies will be carried out in liver and bladder cell systems as well as in systems employing partially purified enzymes. These experiments will be designed to determine the nature of the reactive intermediates involved in the observed nucleic acid binding and unscheduled DNA synthesis. In addition to the above carcinogenicity study, a short-term toxicity study will be conducted in rats in order to gain additional information concerning the metabolic activation of phenacetin.

From 08/01/79 - 07/31/81 FY 81: 0 (Ann. \$53,292)
Dr. Lincoln Polissar, Fred Hutchinson Cancer Research Center,
Seattle, Washington 98104

Objectives: The analysis of cancer patient referral patterns in the Puget Sound Region will promote improvements in the referral process by providing people involved in health care a quantitative framework for action and planning, with resulting benefit to patient, physician and community in terms of high quality, cost-effective care. The specific findings of the study will also be an advance in knowledge about factors that affect the choice of care location. The study will also have national significance through the development of a guidebook for analyzing and describing hospitalization flows in other areas of the country.

Accomplishments: Analysis of the place of hospitalization for invasive cancer cases diagnosed in the 13-county study area in the Puget Sound Region during 1974-1979 is completed. The analysis reveals a trend toward increasing use of hospitals in the home county and a decreasing use of distant hospitalization in Seattle, the dominant referral center in the area. This trend was most marked outside the major referral centers, King and Pierce counties. In these two counties, over 90% of the resident cancer patients received all of their hospitalization in the home county, and this was virtually unchanging through time. In the other eleven counties the proportion of patients receiving all hospitalization in the home county increased from 47% to 56% between 1974 and 1978. Our analysis indicates that radiation and other treatment facilities are dominant factors in determining the proportion of patients who stay in the home county for hospitalization. The trend in increasing hospitalization within the home county was most dramatic in the two counties that established radiation treatment facilities during the 1974-1979 period. The second dominant factor is age; there is a monotonic increasing trend of hospitalization outside of the home county with decreasing age of the patient.

As a case study, we have also analyzed referral patterns for local stage non-micro-invasive cervical cancer. The tumor at this stage requires a highly specialized surgical procedure and surgeons skilled in the operation are based only in Seattle. We have found that almost all patients in the area are referred to one of these surgeons for the procedure. On the other hand, we have found that a number of micro-invasive cervical cancer cases are needlessly referred into Seattle for the relatively standard surgery.

Dr. Jerry Schneider of our project has completed a computer mapping program for displaying flows of patients between areas. A "menu" allows the user a number of display options. The flow maps are effective in presenting data in a way that is easily assimilated. As part of our dissemination effort, Dr. Schneider will be demonstrating the use of the flow map program at a national medical care conference later this year.

Plans: Preparation of a description of the current referral patterns and a set of referral rates that characterizes each community is planned. Rates will also be calculated for categories of the major factors affecting referral. A guide-

Program Director: Margaret E. Holmes, Ph.D.

book providing health care planners with the methodology for assessing their own referral patterns will be completed.

From 07/01/79 to 06/30/84

FY 81: \$71,619

Dr. Charles A. Coltman, Jr., The University of Texas Health Science

Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, Texas 78284

Objectives: The multidisciplinary clinical cancer education program is designed to improve cancer education at the University of Texas Health Science Center at San Antonio by: (1) defining the oncology curriculum; (2) applying a systematic testing of the curriculum; (3) improving didactic teaching; (4) developing dial-access audiotapes on the diagnosis and management of malignant diseases; (5) implementing clinical assistant and associate programs; (6) conducting new seminars, continuing education programs and organ-site outreach programs.

Accomplishments: (1) Definition of the oncology undergraduate curriculum in the form of behavioral objectives. The objectives, along with self-assessment test questions and answers, are being developed into an "Oncology Objectives and Review Manual." (2) Development of a computer managed oncology test item bank and annual administration of an "Oncology Test" to graduating seniors to assess the level of cancer related knowledge that our graduates possess. Data obtained from analysis of test scores will be used to identify strengths and deficits in the undergraduate curriculum. (3) Annual analysis of our students' performance on the oncology items of NBME Parts I and II. (4) Development of scripts for the dial-access audiotapes on a variety of tumor categories and paraneoplastic syndromes. (5) Implementation of the Clinical Assistant Program. To date, seventeen students have completed six-week oncology related laboratory and clinical research projects. Of these projects, two resulted in paper presentations of the students' data at national meetings and two journal publications. Additional projects have been approved for the present fiscal year. (6) Implementation of the Clinical Associate program, supporting a total of eight fellows to date. (7) Development and implementation of an Advanced Clinical Oncology course for medical and surgical residents and fellows. Detailed objectives were developed for the course as well as a pre/post test to assess Knowledge gains of participants. Classes meet weekly for a period of nine months. (8) Implementation of an Annual Breast Cancer Week. Activities during the week included a Breast Cancer Symposium for Physicians and Nurses and community activities to heighten public awareness concerning the detection and treatment of breast cancer.

Plans: Publication of the Oncology Objectives and Review Manual; development of instructional materials related to oncology objectives; development of additional audiotapes and implementation of the dial-access audio system; development of additional test items for the oncology test item bank and continued maintenance of the bank; continued administration and analysis of the annual Oncology Test and analysis of NBME scores; continued implementation of the Advanced Clinical Oncology Course, Clinical Assistant and Associate Programs, and Continuing Education Programs.

Program Director: Margaret H. Edwards, M.D.

Grant 26071: Predictive Value of Wolfe Classification in Breast Cancer
Detection Demonstration Project Women

From 09/30/79 to 07/31/82 FY 81: \$438,454
Dr. T. Carlile, 1000 Seneca St., Virginia Mason Research Center, Seattle,
Washington 98101

Objectives: 1) To determine if radiologists can classify mammograms accurately according to Wolfe, with results that are reproducible and show both inter and intra observer consistency.

2) To determine if the Wolfe System of classifying parenchymal patterns for both film-screen and xeromammography (XR) is related to the subsequent risk of developing breast cancer within a period ending 7 1/2 to 9 years after a negative screening examination.

3) To assess the interrelationships of the Wolfe classification with other breast cancer risk factors.

Accomplishments: 1) The Reproducibility Consistency Study (R/C Study) was designed to test the ability of radiologists to classify mammograms in a reproducible and consistent way. Three studies were set up, consisting of three different sets of 100 mammograms. In R/C I, eleven radiologists (1 of 12 was on sabbatical in England) read their home mammograms and the exchange mammograms from the institution using the same modality, film or XR. The study was completed by a third reading of the home mammograms for consistency. The average exact consistency for the four classes was 75%. Exact-minor consistency (P2, DY, or NL, P1 minor) (P2 or Dy to N1 or P1 major) was 87%. R/C II was repeated with a new set of 100 mammograms classified by twelve radiologists after 11 of 12 had taken John Wolfe's course in which some time was spent on the Wolfe classification. Exact consistency was 78%. Exact and minor inconsistency was 91%. R/C III used a third set of 100 mammograms prior to using the newly developed atlas. Exact consistency was 80%. Exact and minor inconsistency was 92%. The post atlas phase of R/C III has not been completed. The above findings represent a high degree of accuracy as related to other x-ray procedures. 2) The Case/Control Study (CA/CO Study) has been structured, forms developed and personnel trained for interviews. Data forms have been completed on incident cancers from the BCDDP screens of years 2-3-4 and 5, and new cancers in years 6-7. A total of 410 triads have been entered into the Data Bank for analysis.

Over 90% accountability is being maintained of the four BCDDP populations. Developing incident cancers are verified pathologically. The project pathologists review all cases.

The project radiologist classifies the mammograms of the incident cancer and two matched controls according to the parenchymal pattern. Other risk factors are updated from the annual interviews. Completed forms are sent to the Data Coordinating Center.

Program Director: Richard D. Costlow, Ph.D.

3) The Data Coordinating Center (DCC) is operational. A procedural manual has been written for implementation of the R/C Study and for the CA/CO Study. Statistical analyses of data from the first and second R/C Studies were made available to participants for study. A preliminary analysis of the 410 triads of the CA/CO Study was presented with co-variables for study.

Plans: The third R/C Study will be completed to measure the effect of the atlas. The total population of the 4 BCDDP's will be followed to identify developing incident cancers and enter them into the study. Prevalent cancers and cancers in women with a mastectomy prior to entry will be added to the CA/CO Study in the third year. Detailed analysis of results will be made and reports compiled to determine the predictive value of the Wolfe classification and its inter relation with other risk factors.

From 07/01/79 to 06/30/84 FY 81: 48,525
Dr. Gerald Shklar, Harvard School of Dental Medicine
188 Longwood Avenue, Boston, Massachusetts 02115

Objectives: The program in oral oncology is designed to improve the chances of survival and the restoration of optimal oral health by education of dental students, postdoctoral students and clinical associates in oral oncology, as well as dentists, physicians and auxiliary health personnel. Specific objectives involve dental curriculum enrichment by presentation of a course on oral medicine and oral oncology, rotation of predoctoral and postdoctoral students through the dental department of a cancer institute (Sidney Farber Cancer Institute) and the development of specialists in oral oncology by postdoctoral experience in radiation therapy, oncologic medicine, surgical oncology, as well as oral management of the cancer patient, including dental procedures and the management of oral problems secondary to radiation, chemotherapy and surgery. Continuing education of dentists and physicians in oral cancer is carried out by presentation of lectures, courses and by oral cancer screening programs in the community. Development of teaching materials, including illustrations of cases, will facilitate future educational ventures in oral oncology. A syllabus will stress the multidisciplinary approach to oral cancer, with sections prepared by radiation therapists, surgeons, chemotherapists, maxillofacial prosthodontists, epidemiologists, pathologists, dermatologists, otolaryngologists and others.

Accomplishments: (1) Development of a core curriculum course in oral oncology, offering a multidisciplinary approach. Guest lecturers include eminent specialists in radiation therapy, oncologic medicine, surgery, etc. from Harvard Medical School and Harvard School of Dental Medicine, Sidney Farber Cancer Institute, Massachusetts General Hospital, Brigham & Women's Hospital and Children's Hospital Medical Center. (2) Development of rotations in oral oncology at the Sidney Farber Cancer Institute under the direction of Doctor Stephen Sonis, Chief of Dental Service. (3) Development of postdoctoral experience in oral oncology. Three clinical associates are presently receiving support. (4) development of oral cancer screening programs in the community, providing public education and continuing education of dentists and physicians. (5) Development of a syllabus on oral oncology. This will eventually be published as a textbook of oral oncology.

Plans: (1) Further development of the program in oral oncology so that a more varied experience will be available to the associates in oral oncology who are appointed to the program. (2) Further development of the predoctoral course in oral oncology and self-teaching materials. (3) Preparation of a textbook on oral oncology, with some twenty chapters. Chapters will be prepared by those specialists who have been lecturing in the oral oncology course and who have been responsible for the postdoctoral teaching in the elective clerkships.

Program Director: Margaret H. Edwards, M.D.

From 09/30/79 to 07/31/82

FY 81: \$98,154

Dr. Anna Meadows, Children's Hospital, 3400 Civic Center Boulevard
Philadelphia, Pennsylvania 19104

Objectives: The recent development of aggressive multi-model therapies for childhood cancer, usually accomplished with university-affiliated cancer centers, has led to improved survival rates, but it is also associated with a variety of late effects which are often subtle and delayed. There is a significant lag time, both for dissemination of information about new advances from cancer centers to community physicians, and for problems in after-care and disease/therapy-related sequelae noticed in the community to be reported back to the cancer center. Therefore, a project aimed at facilitating the exchange of pediatric cancer information between cancer centers and community physicians is being conducted, in the hope of improving the delivery of primary and continuing care for these children, and of establishing a model program for adult cancer information exchange.

Accomplishments: Five-hundred fifty physicians within the Greater Delaware Valley and in peripheral areas, who potentially care for children with cancer, were identified. A letter and a one-page questionnaire was sent to each physician requesting information regarding referral patterns, assessing their interest in participating in a program of information exchange with the Cancer Center, and determining areas of interest to participants.

The overall response rate to the initial mailed questionnaire was 59%. Respondents indicated a high level of interest in pediatric cancer diagnosis, treatment, acute and late complications, outcome, as well as other areas, particularly psychosocial support for the patient and his/her family. Physicians were asked to indicate their preferences as to methods of information exchange. Communication via information bulletins was the most popular medium; although 40% expressed interest in more personal exchanges through Cancer Center/community workshops and telephone "hotlines."

A Cancer Center-based workshop, held on January 28, 1981, brought physicians most active in caring for children with cancer together with cancer center staff to identify areas to be highlighted in the program. Sixteen community physicians from hospitals with and without university medical school affiliation attended. Presentations were made relative to the Children's Cancer Research Center's programs in epidemiology and etiology, survival, late effects, and psychosocial support systems. Through discussion of care problems encountered in their practices, community physicians reaffirmed their interest in the Program, particularly with regard to information on current therapies, methods of monitoring late effects, and developing psychosocial support systems. Community physicians expressed a desire for additional information concerning patients whose care they manage in conjunction with the Center. A form which specifies the patient's diagnosis, treatment regimen, Cancer Center physician and social worker will be forwarded to referring physicians. In discussing methods of exchange, community physicians expressed a preference for periodic Cancer Center newsletters focusing on specific management issues in pediatric oncology.

Program Director: Donald N. Buell, M.D.

Volume 1 of the "Pediatric Oncology Newsletter" presents notes from the recent Children's Cancer Study Group Meeting concerning changes in protocol, results of trials, and proposals for new studies. A protocol for evaluating the health status of long-term survivors is included. At the workshop, Community physicians were also surveyed in order to characterize their sources of medical information about pediatric cancer protocols (100%) and colleagues (92%) were the most valuable sources of pediatric cancer information. Local conferences (57%), national meetings (29%), and medical journals (21%) were less useful.

Criteria for critical process measures have been developed for three neoplasms (Wilms' tumor, medulloblastoma, and acute lymphocytic leukemia) to serve as models for evaluating the extent to which diagnosis and therapy outside the Cancer Center approximate that which takes place in the Center. Record review in community hospitals has been completed. Preliminary results of these surveys show better survival within the Center for medulloblastoma (3 yr. survival 48% vs. 74%). For Wilms' tumor, survival is the same when Cancer Center is compared with community hospitals, although cancer centers perform more diagnostic evaluations and treat somewhat differently. However, community-based stage 1 Wilms' tumor patients continued to receive radiation therapy in the face of National Wilms' Tumor Study (NWTs) results which found post-operative radiation therapy unnecessary in young patients with early stage disease. Results of these surveys also confirm the previously described need for community physician education regarding methods of evaluating the health status of long-term survivors.

Plans: Data from the surveys of outcome, evaluation, and treatment will be further analyzed, weak points in care identified, and educational programs to correct deficiencies will be implemented. Topics of interest to community physicians will be addressed in the quarterly "Pediatric Oncology Newsletter." Plans will be initiated for a workshop to be held in the fall of 1981, which will present more didactic information regarding issues in pediatric oncology. The effectiveness of the Program will be assessed by monitoring survival and quality of survival of patients treated in the community and the Center.

From 07/01/80 to 06/30/82

FY 81: \$121,748

Dr. S. Stephen Kegeles, University of Connecticut, Department of
Behavioral Sciences and Community Health, Farmington, Connecticut
06032

Objectives: The major objective of this research program is the development of cost-effective, feasible methods for the encouragement of regular, monthly breast self-examination (BSE). Using a behavioral analysis of BSE as a theoretical framework, the research tests the effectiveness of stimulus control (cueing) and reinforcement control (reward) techniques in two consecutive prospective experiments of six months each with six-month follow-ups. Both frequency and accuracy of BSE performance are being assessed. The results will indicate whether such techniques are differentially effective for women with varying social psychological and background characteristics, including risk factors and prior experience with BSE.

Accomplishments: During the second year, the first experiment was completed. Two kinds of stimulus control techniques were tested: self-managed cues (calendars and reminder stickers) and an external cue (postcard). One quarter of the sample was provided both kinds of cues, one quarter either one or the other, and one quarter neither. The 215 volunteers, randomly assigned to conditions, are patients of the Family Medicine and General Medicine practices at the UCHC. Participants were taught BSE and interviewed, followed for six months, and then seen again when they were asked to demonstrate their BSE technique and re-interviewed..

In order to determine the representativeness of the study group, a telephone interview using questions comparable to the participant interview was conducted with 100 randomly selected women.

Preliminary analyses indicate that participants in the study differed from refusers in that they reported: fewer BSE's in the prior six months, greater likelihood of a history of breast problems and of family cancer and better general health. Participants were also somewhat younger ($M=44.1$) than refusers ($M=49.8$), more likely to express beliefs in controllable outcomes and in the efficacy of breast self-examination.

During the six-month study period, self-reporters of four-six BSE's increased dramatically for the entire group of participants, from 21 percent to 62 percent with 48 percent verified by monthly record returns. Although cyclic (menstruating) women in general did fewer BSE's, self-management was effective in increasing their frequency to a level comparable to non-cyclic women. Overall, postcards also tended to increase frequency.

Plans: During the third and final year, the second experiment, which tests rewards will be completed. The influence of background factors on BSE acceptance will also be examined in detail. In addition, data relevant to accuracy of BSE will be analyzed. A competitive renewal grant to test additional interventions and refine and extend our findings will be submitted.

Program Director: Sandra M. Levy, Ph.D.

Grant 26235: Control of Emotional Distress in Cancer Chemotherapy

From 05/01/80 to 04/30/83

FY 81: \$150,800

Dr. Howard Leventhal, University of Wisconsin, Madison, Wisconsin 53706

Objectives: The project is designed to examine the psychosocial consequences of chemotherapy for patients with breast cancer or malignant lymphoma. The study focuses on the side effects that patients experience during chemotherapy, their interpretations of these side effects, their efforts to control them, and the criteria by which the treatment is seen to be effective. Following data analyses to determine which of the above factors contribute to emotional distress during treatment, an intervention study will be conducted to evaluate patient education procedures designed to reduce distress.

Accomplishments: In the first three months of the grant period, we designed, pilot tested, and revised five interview forms: an initial interview to assess patients' feelings and expectations about treatment before it begins, and four follow-up interviews to be conducted after the first, second, third, and sixth cycles of treatment. We also devised a daily diary form on which patients could keep detailed records of treatment side effects and emotional states.

Data collection began in June of 1980 at the U.W. Hospital and Clinics, and we began making arrangements at that time to recruit patients from the Dean, Jackson, and Quisling Clinics in Madison, as well as from the V.A. Hospital here. As of March 15, 1981, we had recruited 121 patients to the study. Over 300 interviews have been conducted, and most have been transcribed onto written interview records. We are beginning the process of numeric data coding for computer storage and subsequent analysis. To date, we have had 10 patients refuse to participate in the study, four patients who were eligible but whose physician requested that they not be approached about the study, and five patients who have died before completing the entire set of interviews.

We have also conducted a small-scale study to examine the factors associated with conditioned nausea and vomiting in patients receiving cis-platinum therapy for ovarian, testicular, and bladder cancer. We have interviewed 32 patients on this study and have completed preliminary data analyses.

Plans: Data collection will continue on the main longitudinal study until December of 1981, when we expect to have approximately 100 patients in the lymphoma sample and 200 women in the breast cancer sample. At that point, complete data analyses will begin, and results will be incorporated as soon as possible into the design of intervention studies. The intervention studies, which we may start in a pilot phase even before complete data analyses are available, will occupy the remainder of the grant period.

Program Director: Sandra M. Levy, Ph.D.

Publications:

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Leventhal, H., and Nerenz, D.R.: A model for stress research and some implications for the control of stress disorders. In D. Meichenbaum and J. Jarenko, eds., Stress Prevention and Management: A Cognitive Behavioral Approach. New York: Plenum Press, in press.

Grant 26292: Pain and Anxiety in Children With Acute Leukemia

From 07/01/79 to 06/30/82

FY 81: \$42,773

Dr. Jonathan Kellerman, Childrens Hospital, 4650 Sunset Boulevard,
Los Angeles, California 90027

Objectives: This study was designed to evaluate the efficacy of training in hypnosis in reducing pain and anxiety in children with acute lymphoblastic leukemia (ALL) undergoing bone marrow aspirations (BMA's). As proposed, patients/subjects were selected from the population of children between the ages of 6 and 10 years of age with ALL, receiving outpatient treatment in the Division of Hematology-Oncology at Childrens Hospital of Los Angeles. The design calls for randomization of 40 patients to either hypnosis or attention/placebo groups with stratification of the sample of sex. Baseline measures are collected along three dimensions: behavioral observation, nurse ratings, structured self-ratings of pain and anxiety. Two training sessions are offered post-baseline and prior to the next outpatient bone marrow aspiration. Further sessions are provided prior to each of three post-baseline bone marrow aspirations and response to training is monitored using the three dependent measures.

Accomplishments: Accrual of patients continued. Fifteen patients accrued to this study during this reporting period. Seven were randomized to the hypnosis group, eight to the comparison group with a total sample size of 32 (16 hypnosis, 16 comparison). Stratification by sex was carried out, as in year -01, leading to an equal distribution of males and females in each group (11 males, 5 females). The preponderance of males in the sample reflects an incidence pattern in ALL. Attrition occurred for two reasons. Two patients in the hypnosis group died and one patient in the comparison group moved away from the geographical area covered by Childrens Hospital of Los Angeles. At present, the number of active patients is 29 (14 hypnosis, 15 comparison). Baseline data were collected for all patients. Pre-procedural training was completed for 27 of 29 patients (93 percent) with two patients still training. To date, seven patients have satisfied the criterion for going off-study (three post-training bone marrow aspirations) four in the hypnosis group, three in the comparison group. Nine patients have undergone two post-training BMA's (five hypnosis, four comparison), seven have undergone one post-training BMA (one hypnosis, six comparison). There were no procedural problems or alterations in the proposed methods of patient acquisition and intervention, nor did methodological changes take place.

Plans: As proposed, patients will continue to accrue to the study for all of Year II and the first half of Year III. Data analysis will be conducted in Year III. Patient accrual has proceeded at the predicted rate and there have been no methodological or pragmatic problems with the research design. Thus, it is predicted that the full sample of 40 children will have accrued by the second half of Year III at which point data analysis will begin.

Program Director: Sandra M. Levy, Ph.D.

Grant 26362: Bladder Cancer Risk Factors in Utah

From 09/30/79 to 05/31/82

FY 81: \$74,427

Dr. Dee W. West, University of Utah Medical Center, Salt Lake City, Utah

Objectives: This project is a continuation of a 12-month epidemiological study of bladder cancer conducted in 1978 by NCI. Continuation of this case-control study in Utah will allow us to interview enough cases (about 380) to meet the following objectives: (a) test for an association between coffee consumption and bladder cancer (this can be studied easily in Utah since only about 50% of the residents drink coffee), (b) test for an association between caffeine use and bladder cancer (much of the coffee used in Utah is decaffeinated and also caffeinated soft drinks are often used among noncoffee drinkers), (c) look for synergistic effects of coffee and caffeine with tobacco in relationship to bladder cancer risk, (d) determine why bladder cancer is higher in urban areas, (e) determine why the incidence of bladder cancer is increasing among older males, and (f) look for other variables that may be involved in the etiology of the disease.

Accomplishments: Cases are identified through the Utah Cancer Registry (1978-81) which registers all cases of bladder cancer diagnosed in the State of Utah. Controls (two for every case) are selected randomly from the Utah population using random digit dialing. By September of 1981, 360 cases and 740 controls will be interviewed. We expect to interview about 85% of all eligible cases and controls.

Plans: All interviewing will be completed by the end of 1981 and data analysis will begin in early 1982. Results from the study should be published late in 1982.

Program Director: William E. Straile, Ph.D.

Grant 26363: Breast Cancer Detection by Breast Self-Examination

From 07/01/79 to 06/30/82

FY 81: \$104,972

Dr. Roger S. Foster, Jr., University of Vermont, Department of Surgery,
Burlington, Vermont 05405

Objectives: Studies are underway to obtain data to confirm or refute the hypothesis that breast self-examination (BSE) can lead to earlier breast cancer detection and decreased breast cancer mortality. Data is being collected on all breast cancer patients in the State of Vermont with breast cancer newly diagnosed since July 1, 1975, and the frequency of BSE performance prior to breast cancer detection, the clinical tumor-node-metastases stage, the pathologic stage and the mortality rates are being determined.

Accomplishments: The Breast Cancer Network Demonstration Project (BCNDP) has been restructured to serve the function of this breast self-examination (BSE) grant with modification of the prospective data collection to include additional data on such things as method of detection of breast cancer, whether and how the patient had been taught to do BSE and details as to type and time of biopsy relative to definitive treatment.

The registry was updated for the six-month lapse between the BCNDP data collection and this BSE grant data collection (total number of patients 987). The computerization of the data has also been restructured. Collection of all pathologic data in Vermont on benign breast biopsies from July 1, 1975, to present was completed. A follow-up system has been established to determine status of patient, that is, whether the patient is alive or dead, and the cause of death. An alphabetical listing of all Vermont women taught BSE under BCNDP for integration with the breast cancer registry is being established.

Plans: (1) To obtain life-table analysis of survival curves for the three BSE performance categories; (2) to analyze clinical and pathologic stage and histologic type of breast cancers by BSE performance and method of detection; and (d) to perform preliminary analysis of any breast cancers occurring in patients in the BSE instruction registry.

Program Director: Sandra M. Levy, Ph.D.

From 9/30/79 to 7/31/82

FY 81: \$99,119

Dr. Peter Hoon, University of Tennessee, 800 Madison Avenue, Memphis,
Tennessee 38104

Objectives: An estimated 20,000 women were diagnosed as having cervical cancer in 1978. Given that hysterectomy is the most common treatment for this disease, and that the incidence of referral to psychiatrists within 4 1/2 years of the procedure was three to four times higher than for a control group of women (Richards, 1973; Barker, 1968), the significance of this study is clear. It is also interesting to note that the majority of the referrals occurred due to symptoms of depression, the most common psychiatric problem in the United States today. Secunda, Katz, Friedman, and Schulyer (1973), note that depression is the major reason for fully 75% of all psychiatric hospitalizations. It is estimated that at least 12% of the adult population will suffer from an episode of depression severe enough to warrant treatment.

In addition to providing information about the incidence of sexual dysfunction among women receiving hysterectomies or other therapy for cervical cancer, this study will assess the efficacy of modern sex therapy techniques in the treatment of these women, as well as training other health providers in these techniques.

Accomplishments: Approximately 35 patients have been assessed on psychological and physiological measures. Patients were diagnosed in one of seven categories: minimal dysplasia, moderate dysplasia, severe dysplasia, carcinoma in situ, carcinoma in situ (possible invasive), invasive carcinoma (few cells), invasive carcinoma (many cells), and false positive. Patients were also grouped according to their medical treatment and these categories included normal control, false positive, cream, cryosurgery, cold knife conization, simple hysterectomy, radical hysterectomy, and radiation. Patients have been recruited for all categories but the last two.

Preliminary results with analysis of variance across diagnoses indicate no differences in mood state or self-reported capacity for sexual arousability; however, the patients differ in oxygen perfusion through the vaginal epithelium as a function of clinical diagnosis. In addition, there is no indication to date that a medical treatment procedure has any affect upon psychological mood state, but the difference in oxygen perfusion occurs again with regard to treatment groups. This difference in treatment groups most likely occurs because a particular treatment is often associated with a particular diagnosis.

Cervical dysplasia patients were compared with eight healthy, sexually functional controls during baseline and fantasy-produced sexual arousal using vaginal blood flow as the dependent variable. During baseline, the groups did not differ, but during fantasy, the groups differed significantly. Interpretation of this result must await further data collection.

Project Officer: Janet L. Lunceford, R.N., M.S.N.

Finally, the heat dissipation electrode bought for this grant was compared, in normal subjects, with the light probe measure used in most sexual arousal research. The purpose of the comparison was to produce a standard conversion algorithm which would allow greater flexibility and precision of measurement among laboratories involved in this research. Publication of the standardization procedure is forthcoming.

Plans: Major plans for the remainder of the study are: (1) to recruit and assess the remainder of the required subjects; (2) to develop a sexuality program for this group of women. This could involve sexual dysfunction therapy, sexual enhancement, or sex education, in a group or individual setting, both being determined by the needs of the women; (3) to begin training Ob-Gyn residents in sex therapy techniques; and (4) data analysis to show possible disease process effect on physiological and cognitive variables.

Grant 26437: Cancer Hopeline: Information Support System

From 7/1/79 to 6/30/82

FY 81: \$75,030

Ms. Claudia Andrews, McDowell Cancer Network, Inc., Lexington, Kentucky 40536

Objectives: The Cancer Hopeline is a toll-free statewide telephone consultation service for the Commonwealth of Kentucky. Its three main objectives are:

- (1) to provide current accurate information on cancer and cancer related topics;
- (2) to provide appropriate referrals within the community which can assist the caller when additional help is needed; and
- (3) to provide individual and family counseling support services.

Accomplishments: Expansion and improvement of current Hopeline service has been the goal. This has been accomplished by: development and utilization of a patient education materials catalogue made available to physicians, health departments and hospitals in Kentucky; development and utilization of a financial aid manual as a resource for professionals; development and utilization of a Hopeline user survey; successful recruitment, training and utilization of undergraduate students in the areas of family studies, social work and psychology; an increase of 71% of phone calls received from western Kentucky; an increase in the publication of local newspapers of the Hopeline column by 18%; a statewide distribution of eight public service announcements; and 4,200 contacts throughout the state through promotion and educational activities. From July 1, 1980 through March 31, 1981, Hopeline has received 1,112 requests (915 by phone, 130 through the mail and 67 walk-ins).

Plans: (1) Use of student volunteers through the Communications Department at the University of Kentucky in the area of promotion and public relations; (2) co-sponsorship of Cansurmout/I Can Cope support groups with the American Cancer Society; (3) expand Hopeline training to a two-semester course through the University of Kentucky; (4) computerization of Hopeline statistics; and (5) planning and development of a resource guide of cancer services in the state.

Program Director: Thomas Kean

Grant 26540: Characterization of LAI-Defined Pancreas Tumor Antigens

From 06/01/79 to 05/31/82

FY 81: \$57,627

John H. Howell, Ph.D., Roswell Park Memorial Institute, Buffalo, New York 14263

Objectives: The main objectives of this project are twofold:

1. to determine if pancreas tumor-specific antigens are present in the serum and malignant effusion fluid as well as in membrane extracts of human pancreas tumor lines grown in mu/nu mice as defined by the micro-LAI assay. LAI reactive material will be purified and xenogeneic monospecific antibodies will be prepared. The purified antigen(s) and xenogeneic antibodies will be evaluated for use in the immunodiagnostic procedures;
2. To develop, from the above biological sources, a soluble stable antigen preparation for use in our immunodiagnostic studies with the LAI assay. Conventional tumor extracts are variably reactive and have a storage life of only four to six months.

The significance resides in the obvious fact that cancer of the pancreas is a devastating disease with a mortality rate of nearly 100 percent. It has recently climbed to the fourth most common cause of cancer death in this country. Despite much effort, detection remains low (approximately 30 percent). The only effective therapy has been surgical resection of early stage disease indicating a need for improved methods of early differential diagnosis and tumor localization. The micro-LAI assay has proven to be useful for the detection of pancreatic cancer, but it can be further improved with the isolation and use of more purified pancreatic tumor antigens.

Accomplishments: Tumor-associated antigens (TSA) have been isolated from the malignant ascites fluid of three patients with adenocarcinoma of the pancreas. Ammonium sulfate precipitation followed by preparative gel chromatography on a Sephacryl S-300 column yielded an immune-complex rich fraction as determined by Cl_q binding assay. The void volume fraction for the first two samples was subjected to repeated affinity chromatography over an S. Aureus protein A-Sepharose CL-4B column until all protein A binding material was removed. Acid buffer was used to remove this binding material which proved to be predominantly IgG immunocomplexes. Sephadex G-200 chromatography in glycine: HCl buffer (pH 2.5) resulted in the separation of three fractions, A, B and C. All three fractions were tested in the micro-leucocyte adherence inhibition (LAI) assay. It was determined that only fraction B expressed antigenic activity when incubated with leukocytes from pancreas carcinoma patients. Analytical isoelectric focusing (IEF) in four percent polyacrylamide gels revealed an extremely acidic protein in fraction B. Subsequent isolation of the immune-complex fraction from sample three and preparative isoelectric focusing in a granular gel bed proved to be more efficient and less time consuming. Both the acid fraction and the immunoglobulins could be recovered. The three acidic proteins were subjected to analytical IEF and each protein demonstrated an isoelectric point between 2.6 - 2.8. SDS-gradient polyacrylamide gel electrophoresis, in the presence of B-mercaptoethanol, revealed

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that the acid proteins had an approximate molecular weight of 20,000 daltons, and migrated as a single band. The acidic protein from sample three was used to raise xenogeneic goat antibodies and the immunodiffusion studies demonstrated that the antibodies specifically recognized the acid protein material from each patient tested. It is also evident that there is immunologic identity between all three acid proteins. Recently, the xenogeneic goat antibodies have been tested against five other fractionated effusion fluids from pancreatic carcinoma patients. The antibodies reacted with all but one of these patients; however, no acidic material was isolated from this patient and it should be noted that the patient received radiation and chemotherapy two weeks before the ascites sample was removed. It must also be noted that the xenogeneic antibodies recognize some component of normal human serum that is immunologically nonidentical to the acid protein reaction. Orosomucoid, Beta-2-microglobulin, alpha-1-macroglobulin, pancreas oncofetal antigen (POA), human immunoglobulins and albumin are all negative in the immunodiffusion tests versus the xenogeneic goat antibodies. Elemental analysis of the acid material (which presently has been extracted from six out of eight different pancreas carcinoma ascites samples) lends evidence to the fact that the molecule is of lipid nature, but further investigations are necessary.

Plans: Future goals for completion of this project involve purification of the xenogeneic antiserum to the acidic proteins by immunoadsorption and incorporation of these antibodies in direct binding assays. The immunoglobulins isolated during preparative IEF of the immune-complex rich fraction will be purified and used in a mixed hemagglutination assay using all of the pancreas tumor cell lines available as well as colon and lung carcinoma cells. Additional malignant ascites fluids, along with essential non-malignant ascites for controls, will be obtained and investigated for acidic proteins by the previous methods and by two dimensional isoelectric focusing/SDS-PAGE. This will allow us to identify the acidic protein and to "map" the total antigenic components of new malignant and benign immune complexes.

From 07/01/79 to 04/30/82

FY 81: \$57,823

Dr. Gary R. Gunther, Department of Biochemistry, St. Jude Children's
Research Hospital, Post Office Box 318, Memphis, Tennessee 38101

Objectives: The major objectives of this project are to characterize the mechanism of hormone-stimulated discharge in normal pancreatic acini and to compare the discharge pathway and cell surface properties of normal acini with those of a rat pancreatic acinar carcinoma (J.K. Reddi and M.S. Rao, Science (1977), 198: 78-80). Such a study would clarify the series of events leading to exocytosis in the normal cell and identify the specific changes which must be explained by any hypothesis accounting for cellular transformation. Specific hormone-dependent events to be characterized and compared include the release or uptake of Ca^{2+} , changes in intracellular levels of cyclic nucleotides, changes in the methylation of membrane phospholipids and the binding of secretagogues to receptors on the cell surface.

Accomplishments: During the present fiscal year, a study has been conducted on the effects of hormonal stimulation on the two main pathways for phosphatidylcholine (PC) synthesis. Due to a problem in obtaining functional normal rat acini, the work on normal tissue was carried out using guinea pig acini. This area seemed promising since Axelrod and others have shown that one of the pathways, namely the successive Nmethylation of phosphatidylethanolamine, is affected by several membrane-related cellular events. In the present study, the transfer of methyl groups from L-(methyl- ^3H)-methionine into phospholipid was measured in acini in the presence of agents that elicit protein discharge.

The basal rate of methyl group incorporation into phospholipid was found to be 93 ± 3 fmol/ug DNA/min (+ S.E.M., 3 experiments). Optimal doses of secretagogues such as caerulein (a decapeptide analogue of the hormone cholecystokinin), carbamylcholine, or the phorbol ester 12-Otetradecanoyl-phorbol-13-acetate (TPA) rapidly reduced the rate of methylation by 50-80%. This effect was maintained as long as the secretagogue was present, but was reversed by removing the hormone with a competitive inhibitor. The decreased rate could be demonstrated within five minutes of caerulein or carbamylcholine addition and within 15 minutes of TPA addition. The above findings were notable since most cell types undergo an increase in phospholipid methylation upon activation.

The alternate pathway for PC synthesis, via condensation of an α, β - diglyceride with CDP-choline, was measured by incorporation of ^3H -choline into phospholipid. Caerulein, carbamylcholine, and TPA all increased choline incorporation by two- to three-fold in normal acini. During the rest of this year, these studies will be extended to the pancreatic acinar carcinoma to determine if the control of PC biosynthesis is altered in this transformed cell type.

Plans: During the remainder of the project period, emphasis will be placed on the characterization of the pancreatic carcinoma in terms of the specific hormone-dependent events listed above, and comparisons will be made to the

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findings in normal acini. A comparison of specific secretagogue receptors in normal and tumor cells will also be conducted.

Grant 26565: Pilot Study of Pain in Four Selected Cancers

From 03/01/80 to 02/28/83

FY 81: \$219,766

Dr. John T. Bonica, University of Washington, Seattle, Washington 98195

Objectives: To determine the characteristics of pain associated with four selected cancers, including lung, prostate, uterine corpus, and pancreas. Specifically, this project will sample cases from the tumor registry maintained by the Fred Hutchinson Cancer Research Center in order to determine: (a) levels of pain; and (b) pain trajectories in cancer patients.

Accomplishments: This project is currently in the planning stage. Our accomplishments thus far include: (a) reviewing pertinent literature on cancer pain and appropriate research methods; and (b) selecting instruments for determining the levels of pain experienced by subjects. Where standardized instruments are available, changes have been explored to adapt specified instruments for the needs of this particular study. Where inadequacies in available instruments have been noted, new instruments are in the initial stages of formulation.

Plans: In the coming months, we plan to: (a) complete work on instrument selection and formulation; and (b) begin pilot work on interviewing patients and perfecting instruments.

Program Director: Donald N. Buell, M.D.

Grant 26582: A Pilot Study of Cancer Pain

From 09/30/79 to 09/31/82 FY 81: \$175,327
Dr. C. Cleeland, University of Wisconsin, 750 University Avenue
Madison, Wisconsin 53792

Objectives: The three objectives of this project include:

1. The development of instruments sensitive to the presence of pain in cancer, its intensity, and impact on the cancer patient, to use these instruments to conduct a cross-sectional study of pain in cancer patients and to contrast pain in these patients with pain in patients with other diseases.
2. The development of methods of reliably determining the physical basis of pain in cancer patients.
3. Study of the attitudes of health professionals and lay persons towards cancer pain, its treatment, and the relationship of pain treatment to the progression of the disease.

Accomplishments: Accomplishments for the first seventeen months of funding, listed by objective, include:

1. Data have been collected from over 1,000 patients using the pain screening questionnaire. More intensive interviews of patients with pain, identified by the screening questionnaire has begun. An observer-based pain rating scale has been used with over 100 patients and results are being analyzed. Assessment of patient data from rheumatoid arthritis patients (contrast groups) is included.
2. Two classification systems for the physical basis of cancer pain have been examined, combined and field-tested by a physician panel. The system includes different levels of specificity which enables judges to record at a level with which they feel confident. Trained nurse clinicians are attempting to identify pain mechanisms from chart review and from examination of the patient. CSF assays for determination of endogenous peptides have been compared with factorial pain scores and a report has been submitted.
3. A questionnaire has been developed to assess respondents' attitudes and perceptions about the incidence of pain, methods to assess the intensity of pain, and methods to assess, patient coping behaviors. The questionnaire also addresses attitudes concerning the providers' interaction with patients who experience pain and methods to prevent or alleviate pain. Initial data suggest the necessity of specifying procedures used by different professional groups. We are also developing a study to more directly compare health professionals and cancer patients' perception of pain and the degree to which pain is relieved by treatment.

Plans: The sample base for the pain screening questionnaire will be extended beyond our own institution. In-depth interviewing of patients with cancer at four sites will begin. Studies of the reliability of judgment of the physical basis of pain will continue. Sample of physicians and nurses will be interviewed.

Program Director: Donald N. Buell, M.D.

Grant 26619: Nursing Interventions in Nutrition of Cancer Patients

From 7/1/79 to 6/30/82

FY 81: \$109,294

Dr. Jane Dixon, Yale University, 855 Howard Avenue, New Haven,
Connecticut 06520

Objectives: Persons with cancer often develop nutritional complications as a result of their disease or its treatment. The objective of the present project is to conduct a clinical nursing experiment evaluating the effectiveness of two nursing interventions on nutritional status and related variables in cancer patients. Respectively, these intervention protocols will involve nutritional supplementation and pre-prandial relaxation. The anticipated result of this project will be a preliminary system for assessing the malnourished or potentially malnourished cancer patient and prescribing subsequent nutrition interventions. Such a system may enable nurses to improve the nutritional well-being of cancer patients, thus enhancing their response to therapy and the quality of their lives.

Accomplishments: This second year has been a year of grant accomplishment. The study is being successfully implemented, and results in a variety of areas are beginning to be felt.

Procedures for identification and pick-up of potential subjects have been incorporated into the routines of several, diverse clinical settings. The number of subjects entered into the study now stands at 71 as of 3/18/81. Of this number, 41 remain active study participants; the remainder are no longer being followed because of death ($n = 23$), withdrawal of consent to participate ($n = 4$), or other reasons ($n = 3$).

A preliminary examination of selected variables from the first twenty-two subjects to complete the four-month intervention period has occurred. While a small sample size by group severely limits the validity of these early findings, it is notable that among persons receiving nutritional supplements, relaxation, or both, only 22% experienced overall weight loss between the first visit and the ninth visit (approximately four months later); this compares to 75% among subjects receiving neither treatment. Further, among the former group, mean change in Karnofsky performance status indicates slight improvement (+.4); among the latter group the mean change is -2.0. (Subjects who died before completion of the four-month intervention period were not included in this analysis; death rates by group range between 10% and 41%, and are lowest in the group receiving relaxation only and highest in the group receiving both relaxation and nutritional supplementation). These figures, however, are based on a small number of subjects, and they should not be interpreted as predictive of the final analysis.

During this year seven presentations related to the project occurred at national, regional and local meetings. Additionally, a positive impact among local clinicians is evidenced through referrals of potential subjects, and a sharing of clinical information.

Plans: Intake of subjects into the study will continue until September 1981; and all data collection will be completed by January 1982. This will leave ample time for analysis of data and reporting of results.

Program Director: Janet L. Lunceford, R.N., M.S.N.

From 09/30/79 to 09/30/82

FY 81: \$42,406

Dr. Alfred L. Goldson, Department of Radiation Therapy, Howard University Hospital, 2041 Georgia Avenue, NW, Washington, D.C. 20060

Objectives: The major objectives set forth in the intraoperative radiation therapy pancreas project were:

1. To determine the feasibility of intraoperative radiotherapy for pancreas cancer.
2. To determine its best application.
3. To determine its role when combined with chemotherapy and additional conventional irradiation.
4. To determine its local and regional toxicity.
5. To determine its tumoricidal effects on local-regional disease.

Intraoperative radiotherapy has had limited application as a viable treatment modality for malignant disease in the U.S.A. Therefore, our first objective was to establish its feasibility and application for pancreatic cancer. In the majority of radiotherapy treatment regimes doses are usually protracted. Therefore, the toxic effect of high single dose electrons on normal tissues, as well as tumor sterilization, had to be assessed from our phase I studies. Until these questions could be answered we could not clearly determine the final role intraoperative radiotherapy would play in pancreatic cancer. Additionally, we had to determine its additive effects on normal and malignant tissue when combined with chemotherapy and conventional fractionated external beam therapy.

Accomplishments: To date, we have treated 20 advanced stage patients with biopsy proven adenocarcinoma of the pancreas. Twelve patients were males and eight were females. Pertinent preoperative procedures now include hyperalimentation or nasogastric feeding for patients with poor nutrition and unfavorable nitrogen balance. Percutaneous biliary tract decompression before surgery improves the patient's tolerance of surgery and radiotherapeutic procedures, and usually speeds recovery. A bilateral subcostal incision provides the best visualization of the abdomen for exploration and insertion of intraoperative treatment cones. The special safety oriented intraoperative treatment cones have proved most successful in delivering the electron beam to precise treatment volumes.

A single dose of 3000 rad electrons is probably at maximum for a safe single dose with 2500 rad being a preferential dose with minimum toxicity, especially if only a small portion of the duodenum is included. In those few patients who came to autopsy, 3000 rad to tumors greater than or equal to 5 cm in diameter produced massive tumor necrosis but viable appearing cells could be seen microscopically. Analysis of data on these first 20 patients would tend to support the idea that intraoperative radiotherapy represents a "boost"

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dose for unresectable pancreatic cancers, to which should be added chemotherapy and conventional fractionated external beam irradiation.

Plans: The last year of our study will call for 2500 rad intraoperatively, followed by systemic chemotherapy (F.A.M. 2-3 cycles), then 4000 rad in 20 fractions to the primary and regional nodes (TDF=66) via photons or photons combined with electrons.

Publications:

Goldson, A.L.: Techniques and Indications for Intraoperative Radiotherapy of Pancreatic Carcinoma. Chapter in book by Cohn. Masson Company, 1981.

Goldson, A.L.: Single high dose intraoperative electrons for advanced stage pancreatic cancer: Phase I Pilot Study. International Journal of Radiation Oncology Biology and Physics, June 1981, in press.

From 09/30/79 to 05/31/82

FY 81: \$63,416

Dr. G. L. Wright, Jr., Department of Microbiology and Immunology, Eastern Virginia Medical School, Norfolk, Virginia 23501

Objectives: The principal objective of this study is to prepare monoclonal antibodies against prostate adenocarcinoma-associated antigens by the lymphocyte hybridoma technique, and to then use these antibodies to purify and characterize the tumor antigens. The availability of purified antigens and monoclonal antibodies should be potentially useful for the diagnosis, management and therapy of prostate cancer.

Accomplishments: We have completed fusion experiments using splenocytes from mice immunized with the prostate adenocarcinoma cell line: DU145. From 228 hybrid cultures, 12 secreted antibodies that preferentially bound to the immunizing cell line, DU145. It is anticipated that the specificity of these hybrid cell lines will be completed during the coming year. One of these hybrid cell lines, DU83.21, has been extensively characterized and appears to have restricted reactivity to malignant prostate and bladder cells. The binding of these antibodies cannot be blocked by PAP, AFP, CEA, HLA, or DR antigens. Recently it has also been shown to bind to a cytomegalovirus (CMV) transformed human embryonic lung cell line and not to CMV core or structural antigens. Preliminary evidence by membrane immunofluorescence and immunoprecipitation experiments suggests that the DU83.21 antibodies bind to a membrane antigen having a molecular size of 82,000 daltons. The DU83.21 antibodies should be most useful for the immunochemical characterization of human urogenital tumor-associated antigens.

Plans: We plan to complete the characterization of the specificity of the hybrid antibodies prepared to date and those from other fusions presently under, including those monoclonal antibodies produced by fusion of prostate cancer patients' lymph node B-cells with the human myeloma cell line SKO-007. It is expected that a battery of useful monoclonal antibodies will be identified and the most specific used for the purification of the prostate tumor-associated antigen(s).

Publications: No publications have yet resulted from this study although six abstracts have been presented and two manuscripts are in various phases of completion and are expected to be published prior to completion of this project.

Program Director: Andrew Chiarodo, Ph.D.

Grant 26662: In Vitro Evaluation of CMI in Tumor Patients

From 07/01/79 to 06/30/82

FY 81: \$34,805

Dr. Thomas L. Feldbush, Department of Microbiology and Urology, University of Iowa, College of Medicine, Iowa City, Iowa 52242

Objectives: When human lymphocytes are co-cultured with either xenogeneic cells (L-929) or allogeneic cells (K-562), the lymphocytes exert a cytotoxic effect upon the target cells. This may occur without overt lymphocyte stimulation (spontaneous cytotoxicity or NK cell activity) or following stimulation with mitogens or antigens. The major objectives of this project were: (1) to utilize this assay to measure immunocompetence of prostatic cancer patients before treatment and to determine whether therapy influences this immunocompetence, and (2) to determine if a tumor cell extract, derived from patients with prostatic adenocarcinoma could be used to measure changes in tumor specific immunity.

Accomplishments: We have established in vitro assays of CMI using both ⁵¹Cr labeled xenogeneic and allogeneic target cells. To date, 84 patients (21 with benign prostatic hypertrophy and 63 with carcinoma of the prostate) have been evaluated for both spontaneous and mitogen stimulated lysis of the xenogeneic target cells. Longitudinal studies were performed on each patient using frozen lymphocytes. In this way biological variations were avoided.

Recently, we began to evaluate CMI in tumor patients using the allogeneic target cell K-562 (NK cell assay). The lymphocyte subpopulation responsible for this activity is distinct from those involved in the xenogeneic lysis described above. We have also established an assay for the measurement of pre-NK cells in which the lymphocytes are precultured with interferon for 18 hours before mixing with the target cells. It has been shown that NK cell levels fluctuate in tumor patients and may be of diagnostic and prognostic value. We are searching for a similar relationship in prostatic cancer patients and are correlating the study to different treatment modalities.

The future thrust of our investigations is to modify our assays to measure tumor specific immunity. To this end we have shown that lymphocytes, when stimulated with soluble recall antigens (Candida and Streptolysin O), generate cytotoxic cells capable of lysing ⁵¹Cr labeled L-929 cells. We shall begin preparing autochthonous tumor extracts as a source of antigen. Longitudinal studies (lymphocytes collected both before and after surgery) will then be performed with these soluble tumor antigens.

Publications:

Schmidt, J.D., T.L. Feldbush, S.H. Weinstein and W.W. Bonney. 1976. Serum Immunoglobulins in Genitourinary Malignancies. J. Urol. 115:293-295.

Lubaroff, D.M., L. Canfield, T.L. Feldbush and W.W. Bonney. 1977. R3327 Adenocarcinoma of the Copenhagen Rat as a Model for the Study of the Immunologic Aspects of Prostatic Cancer. J. Nat. Cancer Inst. 58:1677-1690.

Program Director: Andrew Chiarodo, Ph.D.

Lande, I.J., T.L. Feldbush, D.M. Lubaroff and W.W. Bonney. 1978. Rat Prostatic Carcinoma, 11095-A: Antigenic Profile (Organ and Tumor Specific). NCI Monograph 49:283-287.

Lande, Ilene J., T.L. Feldbush and D.M. Lubaroff. 1980. Studies on a Weakly Immunogenic Squamous Cell Carcinoma of the Rat Prostate. Invest. Urology 17:419-424.

Lubaroff, D.M., C.M. Reynolds, L. Canfield, D. McElligott and T.L. Feldbush. 1980. Immunologic Aspects of the Prostate. The Prostate (In press).

From: 09/30/80 to 06/30/83

FY 81: \$46,819 (est.)

Dr. Neal H. Steigbigel, Montefiore Hospital and Medical Center, 111 East 210th Street, Bronx, NY 10467

Objectives: The objective is to investigate the association of Streptococcus bovis and carcinoma of the colon. The study will determine if the prevalence of fecal carriage of S. bovis by normal controls changes with time and will investigate the effects of antibiotics and diet on fecal carriage of S. bovis. Biotyping and serogrouping of S. bovis will be conducted in an effort to distinguish strains isolated from patients with colon cancer that may be biochemically different from other subjects.

Accomplishments: Fecal cultures from 24 health subjects were examined; the cumulative carriage rate of S. bovis in these control subjects was 67% over the course of one year. Biotyping of S. bovis isolates as conducted: 76 of 96 (79%) isolates of S. bovis demonstrated the presence of α -galactosidase compared to only 1 of 39 (3%) of other isolates. The pattern of reactions was examined with respect to the source of the isolates. Of the 96 isolates tested, 17 were blood isolates from patients with S. bovis septicemia. One test, β' -glucosidase, was more frequently positive in isolates from patients with carcinoma of the colon or sepsis than in other subjects. The group D antigen was found in 171 of the 189 isolates (90%) of S. bovis.

The results of 200 subjects in a Phase I study confirmed the previously demonstrated association of fecal carriage of S. bovis with carcinoma of the colon and failed to demonstrate any association of fecal carriage of S. bovis with GI carcinomas of other than colonic origin. Studies on the quantitation of S. bovis in fecal specimens and the effect of diet on fecal carriage rates have just been initiated.

Plans: Studies in progress on fecal carriage rates of S. bovis in patients with non-colonic gastrointestinal carcinoma and an evaluation of the effect of diet on carriage rate will be completed. Additional strains will be tested to further investigate differences in serogrouping and biotyping of the isolates. Additional patients with inflammatory bowel disease will be added to the study to define the quantitative aspects of fecal carriage of S. bovis.

Publications: None

Program Director: Vincent J. Cairoli, Ph.D.

From: 09/30/80 to 06/30/83

FY 81: \$97,212

Dr. Eleanor E. Deschner, Memorial Sloan-Kettering Cancer Center, 1275 York Ave.,
New York, NY 10021

Objectives: This proposal seeks to determine if the previously described acute proliferative response of colonic epithelial cells in CF₁ mice to 1,2-dimethylhydrazine (DMH) is related to carcinogen-induced neoplasia or to a non-specific reaction of tissue repair after contact with a cytotoxic substance. The specificity of the response will be tested initially by determining if it can be correlated with the degree of carcinogenicity of various mouse strains to DMH. Confirmation of the role of DMH metabolism as the major factor will be obtained using methylazoxymethanol (MAM), the major activation product of DMH. Moreover, evaluation of chemotherapeutic agents known to be non-intestinal carcinogens yet capable of injuring the intestinal mucosa, will be undertaken to resolve further the specificity of the proliferative response to discriminate between organotropic carcinogens and alkylating agents and antimetabolites.

Accomplishments: Five strains of mice with varying sensitivity to DMH have been investigated, CF₁ and SWR (DMH sensitive), AKR and DBA (DMH resistant), and C₅₇ (moderately resistant). Resistant strains displayed a compensatory surge in DNA synthesis at 3-4 days after DMH injection comparable to that seen in the sensitive CF₁ and SWR strains, indicating similar cytotoxicity. Compared with the suitable control group one week following the 6th injection of DMH, enlargement of the proliferative compartment occurred in all carcinogen treated mice. However, expansion of the zone of DNA synthesis was further up the crypt in the DMH-sensitive CF₁ and SWR strains. The proliferative compartment in these mice had expanded fully 20-30% beyond that seen in the resistant strains. Only the DMH-treated CF₁ and SWR strains had ³HTdR labeled cells in the upper third of colonic crypts.

When labeling indices at this time interval were examined, it was determined that DMH-resistant DBA and AKR mice treated with the carcinogen expressed normal control levels of colonic epithelial cell proliferation. In contrast, the DMH-sensitive CF₁ and SWR strains showed markedly elevated DNA synthesis values. Again, only these two sensitive strains had L.I. 20-50% higher than their respective controls.

A shift in domination from the basal third as the major zone of proliferative activity in the crypt to the middle third was seen only in the sensitive strains. However, the phenomenon appears in greater evidence in the CF₁ line than in the SWR mice.

Plans: Experiments using MAM against the same five mouse strains employed in DMH studies are currently in progress. Various antimetabolites and alkylating agents will be provided weekly to CF₁ mice to determine differences in response between them and organotropic carcinogens. Lastly, modification of the acute response to DMH will be attempted using promoters or inhibitors to assess at which stage of the damage and repair cycle these additives function.

Publications: None.

Program Director: Vincent J. Cairolì, Ph.D.

From: 09/30/79 to 05/31/82

FY 81: \$71,520

Dr. Andrea Quaroni, Massachusetts General Hospital, Boston, MA 02114

Objectives: To compare the growth regulation in vitro of normal and tumor intestinal cell lines established from rat intestine, and to study the susceptibility of normal epithelial cell lines derived from different portions of rat intestine to chemical carcinogenesis. The availability of tumor intestinal cell lines will enable us to study, under well defined experimental conditions, the changes in growth regulation associated with malignancy and to define the cellular and biochemical reasons for the known differences in regional incidence of spontaneous and experimentally induced tumors observed in vivo.

Accomplishments: Two different epithelial cell lines have been established from germfree rats: IEC-17 derived from the duodenum, and IEC-18 from the ileum. These two cell lines have a very similar morphology and ultrastructure, a normal rat diploid karyotype, similar growth rates, density inhibition of growth, lack of growth in soft agar, low plating efficiency at low cell density, inhibition of growth by a specific inhibitor extracted from intestinal villous cells and by glucocorticoids, and a similar but not identical set of cell surface antigens, as detected using monoclonal antibodies specific for intestinal cell surface proteins in vivo. Cytotoxicity was assessed by different criteria following exposure to various concentrations of benzo[a]pyrene (BP) and 7,12-dimethylbenz[a]anthracene (DMBA). BP was apparently metabolized at similar rates in IEC-17 and IEC-18 cells; in contrast, DMBA, was metabolized at a rate 10-15 times greater in IEC-18 than in IEC-17 cells. The results so far obtained suggest that cultured epithelial cell lines derived from different portions of the intestinal tract have similar, but not identical properties in vitro, and may be very different in their response to chemical carcinogens. In order to establish tumor cell lines from dimethylhydrazine (DMH)-induced tumors of the small and large intestine, three groups of ten rats have been administered DMH subcutaneously (20 mg DMH/kg body weight) for 12 weeks (1 injection/week). Clinical symptoms of intestinal tumors (weight loss, bloody stools) were observed first 7-8 months after the first injection. The tumors were resected and divided into 3 equal portions for histological examination; for detection of specific cell surface antigens on the tumor cells by immunofluorescence using 23 different monoclonal antibodies specific for intestinal cell surface antigens; and, for the establishment of tumor cell lines in culture. Primary cultures have been obtained following dissociation of the tissue with trypsin/collagenase, or by explant culture.

Plans: To establish and characterize new epithelial cell lines from different portions of germ free rat intestine; to study carcinogen metabolism in the available intestinal epithelial cell lines (IEC-6, IEC-17, and IEC-18); to demonstrate the appearance of tumorigenic cells in cultures of intestinal epithelial cells treated with carcinogens and tumor promoters; to establish and characterize intestinal tumor cell lines from DMH-induced tumors of the small and large intestine; and, to characterize newly developed fetal intestinal organoid cultures, and study their susceptibility to chemical carcinogenesis.

Publications: Quaroni, A. and May, R.J.: Establishment and Characterization of Intestinal Epithelial Cell Cultures. In Methods in Cell Biology, Vol. 21B, C.C. Harris, B.F. Trump, and G.D. Stoner, Eds. New York, Academic Press, 1980; pp. 403-427.

Program Director: Vincent J. Cairoli, Ph.D.

From 07/01/79 to 04/30/82

FY 81: \$137,188

Dr. Joseph Kovi, Department of Pathology, Howard University College of Medicine, 520 W Street, N.W., Washington, D.C. 20059

Objectives: The objective of this study is to investigate by pretested questionnaires whether dietary and/or lifestyle habits of American black males are related to the high incidence of prostatic cancer. In recent years a number of studies have been conducted to find out the possible correlation between diet and neoplasia. It has been estimated that 80 to 90% of human cancer might be related to environmental factors, among which nutrition appears to be one of the most important. The pathways by which nutritional factors lead to cancer might include the possibility that food contains either carcinogens, cocarcinogens, or procarcinogens or that the neoplastic process is caused or enhanced by nutritional deficiencies or excesses. The lifestyle of urban blacks is significantly different from whites and may have a bearing on the higher prostate cancer incidence in the former population group.

Accomplishments: The presently completed analysis is based on 80 age-matched patients and controls. Associations between prostate cancer and the following epidemiologic variables were detected: past history of chronic urethritis, prostatitis or cystitis ($p < 0.01$); exposure to pre-antibiotic treatment (transurethral irrigation) for chronic urethritis, prostatitis or cystitis ($p < 0.05$); family history of cancer ($p < 0.05$); use of androgens and central nervous system stimulants ($p < 0.01$); use of antihypertension medications and other cardiac drugs ($p < 0.05$); use of antidepressant medications after age 50 ($p < 0.05$). Patients consumed less citrus fruits than controls ($p < 0.05$). More controls than patients consumed other fruits (not citrus) ($p < 0.006$). That fruit group is a good source of Vitamin A. Our data suggests that the amount of vitamin A from other fruits may be important in the prevention of prostate cancer. More patients consumed starchy foods as compared to controls ($p < 0.04$). Patients drank wine less often than controls ($p < 0.01$). These findings suggest that wine may have some protective effect against prostate cancer. The intention of the essentially completed anatomic pathology (necropsy) portion of our study was to confirm or refute the hypothesis that there is a causal relationship between carcinoma of the prostate and aging. Prostate glands with and without carcinoma were examined for the presence of well documented aging changes: medial fibrosis, intimal thickening, smooth muscle proliferation in arteries; sclerotic atrophy of prostatic glands. A total of 795 prostate glands were studied. Our investigation suggests that age per se is not etiologically related to the development of prostate cancer.

Plans: We plan to increase the number of patients with prostate cancer and controls enrolled in our protocol significantly to the completion of the project. To this end an additional large hospital has been already added to our survey area. Our nutritional/epidemiology interviewer will also question the spouses of cancer patients to validate information given by the patients. From larger numbers of patients and controls our conclusions based on the statistical analysis of our data will obviously be much stronger.

Program Director: Andrew Chiarodo, Ph.D.

Publications:

Jackson, M.A., Kovi, J., Heshmat, M.Y. et al: Characterization of Prostatic Carcinoma Among Blacks: A Comparison Between a Low-Incidence Area, Ibadan, Nigeria, and a High-Incidence Area, Washington, D.C. PROSTATE: 1:185-205, 1980.

Duong, H.D., Jackson, M.A., Kovi, J. et al: Mixed Mesodermal Tumor of Urinary Bladder: Light and Electron Microscopy Study. UROLOGY. (In Press).

Jackson, M.A., Kovi, J., Heshmat, M.Y., et al: Factors Involved in the High Incidence of Prostatic Cancer Among American Blacks. In: CANCER AMONG BLACK POPULATIONS (Progress in Clinical and Biological Research Volume 53). Edited by Curtis Mettlin and Gerald P. Murphy. Alan R. Liss, Inc., New York. pp. 111-132, 1981.

Grant 26690: Patterns of Care in Oncology

From 01/01/80 to 12/31/81

FY 81: \$163,442

Dr. Robert E. Greenberg, Dartmouth College, 2 Maynard Street, Hanover,
New Hampshire 03755

Objectives: This is an epidemiologic study designed to study the patterns of lung cancer care in New Hampshire and Vermont and to examine the relationship of these patterns to geographic differences in patient survival statistics and to the availability of specialized cancer treatment facilities.

This study will also test the assumption that identifiable populations in the United States lack easy access to sophisticated cancer treatment facilities and therefore receive suboptimal care and have poorer outcomes.

Accomplishments: Project funded too recently for results.

Program Director: Harry Handelsman, D.O.

Grant 26692: Population-Based Study of Lower Urinary Tract Tumors

From 07/15/79 to 06/30/81

FY 81: \$0 (Ann. \$41,467)

Dr. L.D. Marrett, Yale University, New Haven, Connecticut

Objectives: This is an epidemiologic study of bladder tumor (BT) and other lower urinary tract tumors (LUTT). Our research focuses on the role of potential risk factors for BT and LUTT heretofore inadequately studied, such as passive smoking, skin exposures to therapeutic, industrial, and household products, and use of analgesic medications; previously collected data are being used to estimate and control for the major suspected risk factors for BT and LUTT - namely, smoking, occupational exposures, artificial sweetener and hair dye use, coffee consumption, and source of drinking water. In addition, we describe the patterns of occurrence in Connecticut utilizing the data of the Connecticut Tumor Registry (CTR).

Accomplishments: Comprehensive interviews have been obtained for 128 newly diagnosed cases of LUTT (86 males and 42 females), comprising mostly renal renal pelvis and/or ureteral tumors. In addition, about 250 control subjects and 150 bladder cancer cases previously interviewed have been recontacted by telephone and questioned about their past use of analgesic medications. All data have been coded and most have been keyed. Some preliminary analyses have been carried out using the basic data on bladder cancer cases and controls collected in Connecticut during 1978-79 as part of a large collaborative study. Smoking, occupation, and coffee drinking have been examined in a superficial fashion; preliminary results give odds ratios of 2.7 for males and 1.7 for females associated with smoking (ever vs. never), 0.9 for males and 1.7 for females ever working in an a priori high risk occupation, and 4.0 for males and 1.5 for females ever drinking coffee. During coming months more detailed analyses will be conducted including other variables and using other analytic techniques such as logistic regression.

Plans: As regards the descriptive component, CTR records for 1960-67 diagnoses of kidney cancer with nonspecific histology have been reviewed for any more specific primary site information (e.g. kidney parenchyma, kidney pelvis, or ureter). Primary site will be coded where possible; the remainder will be allocated to either parenchyma or pelvis/ureter using the proportional distribution between the two sites, when known, for each age/sex/year of diagnosis group, and time trends since 1960 estimated. This project is scheduled to terminate in 1981, by which time analysis should be complete and publication reports begun.

Program Director: William E. Straile, Ph.D.

From 09/01/79 to 08/31/84

FY 81: est. \$106,562

Dr. A.P. Kyriazis, University of Cincinnati Medical Center and Scott and White Clinic, Temple, Texas.

Objectives: The purpose of this project is to study the effect of single agent and combination chemotherapy and radiation on bladder transitional cell carcinoma by using the nude mouse-human tumor xenograft system. Our main objectives have been: (1) evaluate any synergistic effect between radiation and chemotherapy, (2) study the effect of single agent and combination chemotherapy in an attempt to formulate treatments that would maximize tumor response, (3) study the effect of timing and sequence of treatments on tumor response, and (4) evaluate the histopathologic picture of treated tumors. It is hoped that answers to these objectives would facilitate the formulation of more effective treatments for both localized and metastatic disease. Tumor lines SW-780, SW-800, RT-4, and BICa-1, all of which represent transitional cell carcinomas at various degrees of differentiation are being tested.

Accomplishments: Using cis-platinum (DDP) as a basic chemotherapeutic agent, our studies showed that there is a strong synergistic effect between radiation and DDP. Keeping the DDP dose constant, tumor response depended largely on the amount of radiation and timing of treatments. Radiation (600r 2qW x 5) following completion of DDP course (5mg/K, 1qW x 4) was ineffective. Synergistic effect was less obvious when DDP was given after completion of radiation. Maximum synergistic effect was observed when DDP was administered at an early stage of radiation treatment. In this group, fractionation of DDP (2.5 mg/K, 2qW x 8) did not alter significantly the observed synergistic effect. It was further observed that the synergistic effect between radiation and DDP was independent of tumor sensitivity to the latter. Tumor response to various treatments was reflected in growth curves and the histopathologic picture which was found to be an extremely sensitive indicator of the effectiveness of the treatment and could be used as a predictor of treatment efficiency and tumor recurrence. In addition to these accomplishments, work is in progress aiming at identifying the effect of combination chemotherapy. We are testing the possible synergistic effect of various combination treatments using DDP as basic chemotherapeutic agent along with cyclophosphamide, 5-FU, adriamycin and vindesine.

Plans: Our efforts for coming months will be aiming at two directions: (1) In view of the extremely encouraging results of "radiation-DDP", identify the optimum sequence of the combination (2) complete the studies on the previously mentioned combination chemotherapy regimens.

Publications:

Kyriazis, A.A. and Kyriazis, A.P.: Preferential Sites of Growth of Human Tumors in Nude Mice Following Subcutaneous Transplantation. Cancer Research 40: 4509-4511, 1980.

Program Director: William E. Straile, Ph.D.

Grant 26767: Postdischarge Crisis in Cancer Patients

From 07/01/81 to 06/30/84

FY 81: \$88,076 (estimated)

Marilyn I. Oberst, R.N., Ed.D., Director of Nursing Research, Memorial-Sloan-Kettering Cancer Center, 1275 York Avenue, New York 10021

Objectives: This exploratory descriptive study is designed to examine attitudes of the cancer patient and spouse (or significant other) to the events surrounding the transition from hospital to home following initial treatment. The specific objectives are to:

1. Describe the magnitude and pattern of crisis development and crisis management experienced by patient and spouse (or significant other) during the immediate postdischarge period.
2. Determine the extent to which perceived readiness for discharge, pre- and postdischarge social support, coping strategies, physical status, complexity of treatment regimen, accuracy of knowledge about illness, selected demographic variables, and congruence of patient/spouse (or significant other) knowledge and attitudes are predictive of crisis development and management patterns in patient and/or spouse during the immediate postdischarge period.
3. Describe the magnitude and pattern of change in effectiveness of social support and effectiveness of coping strategies experienced by patient and spouse (or significant other) pre- and postdischarge.

Subjects will be 40 adult cancer patients and their spouses (or significant other). Data will be obtained by questionnaire and interview of patient and spouse at four points in time: discharge, 7-10 days, 30 days, and 60 days postdischarge. The data will have significance for design and timing of follow-up care programs.

Accomplishments: Preliminary pilot work with two subject dyads has provided some initial impressions regarding the accommodation process following hospitalization for cancer surgery. Three major tasks confronting patient/spouse during this period have emerged from the data.

1. regaining a sense of identity
2. solving specific problems of body functioning
3. learning to care for oneself again.

Plans: Data collection will begin after July 1, 1981, if funding is approved.

Program Director: Jan M. Howard, Ph.D.

From 10/1/80 - 08/31/82

FY 81: \$159,659

W. Bradford Parsons, Director of Cancer Control, Sidney Farber Cancer Institute, 44 Binney Street, Boston, Massachusetts 02115

Objectives: The goal of this study is to learn how to improve the quality of care provided for terminal cancer patients. To accomplish this goal the study aims to determine the relationship that exists between congruence, or agreement among patient, family and physician regarding treatment objectives, and satisfaction with the conduct and outcome of the terminal phase. From data collected on the relationship between congruence and outcome, the study expects to explore the need for developing, implementing and evaluating prophylactic and therapeutic psychosocial interventions to promote congruence and/or satisfactory outcome.

Accomplishments:

1. Consolidation of staff.
2. Review and revision of all forms and questionnaires to be used in data collection.
3. Development of a screening system for all cancer patients at SFCI for potential study candidates, using the computer patient registration and appointment schedule in combination with a review of medical records.
4. Development of a file system to track potential study candidates.
5. Implementation of a tickler file to track patients enrolled in study and to determine critical data collection points.
6. Records maintained on the amount of time involved and personnel required to recruit patients from a terminally ill population to meet projected sample size.
7. Establishment of interdepartmental and professional liaisons crucial to the study.
8. Recruitment and registration of patients into the study, starting on 2/4/81 and averaging 2 new patient enrollments per week. It should be noted that acceptance by both patients and physicians is much higher than in the pilot study.
9. A paper describing the Phase Congruence Project and results of a pilot study has been submitted to the New England Journal of Medicine.

Plans:

1. Continue to enroll eligible patients into study to meet projected sample size.
2. Refine system of tracking medical treatment/activity of registered patients to determine critical data collection points.

Program Director: Lawrence D. Burke

3. Continue data collection for all patients enrolled in study.
4. Computer data entry, processing and analysis.
5. Commence study of potential interventions on basis of data analysis.

Grant 26795: Rural Oncology Demonstration Project

From 9/1/80 to 8/31/83

FY 81: \$97,356

Dr. Anne A. Wasson, Frontier Nursing Service, Hyden, Kentucky 41749

Objectives: The Frontier Nursing Service proposes to demonstrate the ability of the rural community-based health provider to deliver quality, up-to-date cancer care using organized local oncology support services and appropriate, coordinated tertiary referral services. Through the use of a nurse oncologist and health educator, the Frontier Nursing Service (FNS) will provide organized professional cancer education, develop specialized cancer nursing services, improve cancer data management through the maintenance of a tumor registry, coordinate a local hospice program, and improve communications and provide appropriate levels of care while minimizing disruption to the rural patient. Formal evaluation of the project's impact on patterns of patient care, community attitudes and professional skills will be undertaken by contract to a university-based team.

Accomplishments: Year I of the project has concentrated on four (4) major areas. These encompass baseline data, inservice training for health care providers, community education, and improvement of clinical care for cancer patients.

The collection of baseline information, under the direction of the evaluation team from the University of Kentucky, has been divided into two (2) components. These are: (1) a chart review to evaluate the preventative teaching and early diagnostic practices of clinicians in the Primary Care Clinics; and (2) a series of questionnaires administered to all personnel who may have contact or clinical care responsibilities of the cancer patient. These tools were designed to measure attitudes, knowledge, needs assessment, and demographics of the FNS health providers.

The other three (3) objectives were accomplished through the following projects:

1. Two (2) inservice training sessions were presented to nursing staff on cancer related issues.
2. Inservice training on BSE (Breast Self-Exam) was presented to 64 female employees during working hours.
3. A month-long anti-smoking campaign including newspaper articles, radio spots, posters, and a four-session smoking cessation clinic to coincide with the American Cancer Society's Great American Smokeout. Smoking habits of the hospital employees were determined before and after the campaign.
4. A monthly rotating bulletin board featuring education on cancer issues was developed for the Primary Care Clinic.
5. Articles from leading nursing journals were catalogued for easy reference.
6. Clinical care for individual patients was provided through assessment and written care plans developed in conjunction with nursing staff.

Program Director: Graceann Ehlke, R.N., M.N.

7. Changes in pain management have included adequate availability of liquid and rectal narcotics and around-the-clock usage of pain medicine for appropriate patients.
8. The tumor registry was increased by the addition of 39 cancer patients.

Plans: Additional baseline data will be collected, indicating areas of learning needs for the primary care providers. From this data, several continuing education programs will be developed for nurses and physicians. Clinical care, collection of registry information, FSMFN curriculum revisions, and community education will continue to develop and improve. The contracted evaluation team from the University of Kentucky will determine the project's image on the patterns of care, community attitudes, and professional skills of the FNS community.

Grant 26832: Counseling Intervention for Chemotherapy Side Effects

From 09/30/79 to 07/31/82 FY 81: \$39,320
Dr. Gary R. Morrow, University of Rochester, 300 Crittenden Boulevard
Rochester, New York 14642

Objectives: This project is a randomized clinical trial testing the efficacy of the behavioral intervention of systematic desensitization for anticipatory nausea and vomiting in chemotherapy patients. There are three arms to the design--a control arm in which regular clinic treatment is carried out, an experimental arm matched for expectancy and credibility and consisting of a supportive counseling approach, and the behavioral intervention of systematic desensitization. Outcome measures include the frequency, severity and duration of anticipatory nausea and vomiting, anxiety measures, measures of locus of control, verbal samples of affect, and measures of changes in other drug-induced side effects.

Accomplishments: Anticipatory nausea and/or vomiting continues to be found in approximately one of five chemotherapy patients screened. Preliminary results of the first 31 patients completing the intervention and five followup visits indicate systematic desensitization produced a significantly greater reduction in anticipatory side effects than either counseling or no intervention. Preliminary analyses of potentially predictive characteristics that distinguish chemotherapy patients who develop anticipatory side effects from those who do not suggest that patients with anticipatory side effects were: (1) younger; (2) more likely to be taking cis-platinum or actinomycin-D; (3) taking more chemotherapy agents with higher clinically rated emetic potential; and (4) experiencing more pronounced post-treatment side effects. Approximately 7 in 10 patients with anticipatory side effects have attributed their symptoms to such causes as "nerves," "anxiety," "tension," "dread," and "it's in my mind."

Plans: The plans are to complete the randomized trial with a subject acquisition of 27 patients for each of the experimental arms. In addition to examining the efficacy of systematic desensitization for the control of anticipatory nausea and vomiting, a data base of over 700 patients will be gathered to examine side effects such as nausea and vomiting following various chemotherapy regimens.

Program Director: Sandra M. Levy, Ph.D.

Grant 26852: Control of Large Bowel Cancer Following Polypectomy

From 07/01/80 to 06/30/85

FY 81: \$270,378

Dr. Sidney J. Winawer, Memorial Hospital for Cancer and Allied Diseases,
1275 York Avenue, New York, New York 10021

Objectives: This project will determine the benefit, risks, and costs of a surveillance program in persons who have had a pre-existing adenoma identified and removed. It is now generally accepted that there is a close relationship between the development of colorectal cancer and pre-existing adenomas of the colon. Identification and removal of these adenomas has been associated with a reduced risk for colorectal cancer. Current concepts indicate the advisability of close surveillance of this population with endoscopic and radiologic techniques to clear the colon of synchronous and metachronous adenomas to reduce the patient's risk. The frequency of examination, the yield of each examination, the risk to the patient, the cost, and the survival benefit of such a program are not known. The data provided by this study will allow recommendations to be made for general application for guidelines for follow-up surveillance of this high risk group and aid our understanding of the natural history of adenomas.

Accomplishments: A randomized control trial has been initiated after polypectomy in which examinations at different frequencies will be done and in which colonoscopy will be blinded against x-ray. The long-term benefit and cost will be evaluated and the results will be related to the initial presentation, including family and personal risk factors, number of polyps, their histology, site, and distribution.

Organizational meetings have been held to finalize the protocol and to coordinate the efforts of the seven study groups located at the Memorial Sloan-Kettering Cancer Center, Mt. Sinai Medical Center, Minneapolis Medical Center, Milwaukee County Medical Hospital, Massachusetts General Hospital, Cedars-Sinai Medical Center, and the Valley Presbyterian Hospital. The Mallory Institute of Pathology will be the coordinating Center for pathology. Questionnaires, forms and procedures have been finalized and patient accrual has begun.

Plans: Approximately 2000 patients will be entered in this protocol over a period of two years. It is anticipated that this extensive data base will provide an important beginning for longer term studies designed to answer questions about metachronous lesions and survival rates.

Program Director: Dorothy R. Brodie, M.D.

Grant 26868: Counseling Cancer Patients in Coping Strategies

From 09/30/80 to 09/29/82

FY 81: \$45,520

Dr. Peter S. Houts, The Pennsylvania State University, Hershey, Pennsylvania 17033

Objectives: The purpose of this study is to develop and evaluate a counseling program for Gynecologic Oncology Patients shortly after they begin treatment for cancer. This program will have the following features.

1. Patients view videotapes of other gynecologic cancer patients who describe coping strategies which have helped them adjust to their illnesses.
2. Patients are counseled to set goals for how they will implement these strategies in their lives.

Three groups will be studied:

1. A control group which receives regular support from the treatment team.
2. A group which views the videotapes of other patients describing coping strategies and are encouraged by the treatment team to implement those strategies.
3. A group which views the videotapes and also receives individual counseling in setting goals for implementation of coping strategies. Counselors also provide follow-up on goal accomplishment.

Accomplishments:

1. The physician in charge of Gynecologic Oncology at the M.S. Hershey Medical Center, Dr. Roderique Mortel, has agreed to serve as medical director of the project and a plan for integrating the program into the Gynecologic Oncology service has been agreed upon.

This plan is to introduce the experimental manipulation in stages where, for two-month periods, all new patients will be invited to join only one of the groups, i.e. May-June = control, July-August = videotape, September-October = videotape plus counseling. This cycle will then be repeated in order to provide for replication within the experimental design.

2. A videotape has been completed in which five Gynecologic Oncology patients describe coping strategies which were helpful to them in adjusting to their illnesses. These coping strategies are: maintaining normal routines, seeking information from physicians, maintaining mutually supportive relationships with others, and making positive plans for the future. This tape has been reviewed by the Gynecologic Oncology treatment team plus eight patients. Their suggestions are being incorporated.

Accomplishments expected by September 30, 1981 are as follows:

1. The videotape described above will be revised and will be in use with non-control group patients.

Program Director: Lawrence D. Burke

2. Three additional videotapes dealing with coping strategies for chemotherapy, radiotherapy or surgery will be completed, field tested, and in use with non-control group patients (matched to their treatment).
3. An estimated forty patients will be enrolled in the study either as controls or in the videotape group.

Plans: By completion of this project it is expected that 120 patients will have participated in the study. There will be 40 patients in each of the three groups. This estimate is based on an expected average enrollment of two patients per week over the 14-month data collection period. Outcome data will be analyzed and interpreted by the completion of the study.

Grant 26878: Counseling Techniques for Breast Cancer Patients

From 02/01/80 to 01/31/83

FY 81: \$78,810

Dr. Joseph Hyland, The Menninger Foundation, Box 829, Topeka, Kansas 66601

Objectives: To assess the effectiveness of counseling in alleviating the psychosocial difficulties in breast cancer patients - those with mastectomy and those receiving interstitial radium implants. These patients were chosen because of (a) high frequency of occurrence, (b) prevalence of associated adjustment problems, and (c) an evaluation of counseling efficacy has not been done. The study aims to determine if (a) counseling techniques affect the quality of life of such patients, (b) if there are any group differences or individual differences in response to selected counseling techniques.

Accomplishments: As of March 31, 1981, 32 patients have entered the project. The project itself is proceeding satisfactorily, although there has been less than the expected number of patients beginning radiotherapy and thereby entering the project.

Demographic and psychological test data have been collected on a pilot group of 24 breast cancer patients. The findings have been published and presented at national meetings. This study (begun March 1979) was directed toward facilitating the project proper and evaluating the efficacy of the psychological tests. Ten-month follow-up data have been recently analyzed and are being written up.

We have continued to actively inform the lay public and professional groups in the community of the project and its findings.

A published account of the project and its progress to date appeared in the Menninger Perspective, Spring, 1981, Volume 12, #1, Pages 11-14.

Presentations:

A National Forum on Comprehensive Cancer Rehabilitation and its Vocational Implications, Williamsburg, Virginia, November 13-15, 1980. (Content of presentations listed under Publications below.)

Annual Conference of the National Association of Private Psychiatric Hospitals, "Challenges and Obstacles in Psychosocial Research in A Radiotherapy Center," in Boca Raton, Florida, January 12, 1981.

33rd Annual Midwest Cancer Conference: 1) "What a Physician Should Know About the Emotional Reactions of His Cancer Patients"; 2) Panel Member on Psychosocial Support of the Cancer Patient, Wichita, Kansas, March 13-14, 1981.

Plans: One hundred and thirty (130) mastectomy patients will be randomly assigned to one of three time-limited selected counseling techniques or control. The psychosocial effects of the counseling techniques will be evaluated over an 18-month follow-up period. Interstitial radium implantations will be studied similarly.

Program Director: Lawrence D. Burke

Publications:

Hyland, J.M., Novotny, E.S., Coyne, L.: Emotional adjustment difficulties in cancer patients. In Proceedings of A National Forum on Comprehensive Cancer Rehabilitation and its Vocational Implications, Williamsburg, Virginia, 1980, pp. 22-26

Hyland, J.M., Novotny, E.S., Coyne, L.: Counseling interventions in cancer patients with emotional adjustment difficulties. Ibid., pp. 109-113.

Hyland, J.M., Novotny, E.S., Coyne, L., Henrichs, M.: The development of a psychosocial oncology program in a community hospital. Ibid., pp. 128-153

Novotny, E.S., Coyne, L., Hyland, J.M.: Psychosocial effects of cancer for a group of breast cancer patients receiving radiotherapy. Ibid., pp. 149-153.

From 09/01/80 to 05/31/83

FY 81: \$57,135

Dr. Howard A. Reber, Department of Surgery, University of Missouri School of Medicine, Columbia, Missouri 65212

Objectives: The objectives of this project are to determine the effects of acute and chronic exposure to bile acids, ethanol, and aspirin on pancreatic structure and function. This will include direct exposure of the main pancreatic duct to all three agents, as well as exposure of the entire gland to ethanol and aspirin by their systemic administration. We are also investigating whether chronic exposure to some of these agents influences the development of pancreatic cancer in an animal model of that disease. These experiments should add to our understanding of normal pancreatic physiology and the pathophysiology of both pancreatitis and pancreatic cancer.

Accomplishments:

1. We examined the effects of chronic ethanol ingestion on pancreatic function and on the appearance of pancreatic neoplasms in Syrian Golden hamsters treated with the carcinogen N-nitrosobis-(2-oxopropyl)amine (BOP) (20 mg/kg subcu). Chronic ethanol ingestion was associated with significantly less preneoplastic ductal proliferation and fewer neoplastic pancreatic lesions.
2. We showed previously that perfusion of the main pancreatic duct in cats with the bile salt glycodeoxycholate increased the permeability of the duct to monovalent ions. Now we have investigated the permeability of the main pancreatic duct to larger molecules, (fluorescein-isothiocyanate conjugated dextrans, MW 3-40,000) before and after the duct was exposed to the same bile salt. In control experiments insignificant quantities of dextrans were recovered in venous blood draining the pancreatic duct. Exposure of the duct to glycodeoxycholate at physiologic concentrations and pressures made the duct permeable to molecules as large as 40,000 MW.
3. We studied the ultrastructural changes and the effects of 16,16 dimethyl-prostaglandin E₂ on the bile salt damage to the pancreatic duct. We described for the first time the ultrastructure of the normal main pancreatic duct in cats. Exposure to physiologic concentrations of bile salt produced striking alterations in this morphology. Prostaglandin E₂ protected the mucosa from these changes.
4. Mongrel dogs with pancreatic and gastric cannulas were chronically fed aspirin and/or ethanol for nine months. Pancreatic function was significantly more impaired in the animals fed ethanol and aspirin than those fed ethanol alone. Thus volume and bicarbonate output in response to submaximal secretin stimulation was decreased about 30% in the ethanol-aspirin dogs, but was increased up to 60 percent in the animals fed ethanol.

Program Director: William E. Straile, Ph.D.

Plans: All of the studies outlined are being pursued. The paths taken by the large molecules that leak from the damaged ducts are being elucidated. The factors which influence the pancreatic secretion of aspirin and related compounds are being studied.

Publications:

Reber, H.A., Mosley, J.G., Fox, J.N.: Effects of aspirin plus ethanol on the pancreatic duct mucosal barrier. Surg. Forum 30:414, 1979.

Mosley, J.G., Reber, H.A.: Effects of aspirin on pancreatic function. Surg. Forum 30:412, 1979.

Fox, J.N., Austin, J.L., Reber, H.A.: Effects of aspirin and pH on permeability of isolated perfused pancreatic duct. Surg. Forum 30:410, 1979.

Reber, H.A., Mosley, J.G.: The effect of bile salts on the pancreatic duct mucosal barrier. Brit. J. Surg. 67:59, 1980.

Tweedie, J.H., Reber, H.A.: The cytoprotective effect of cimetidine on bile salt induced damage to the pancreas. Surg. Forum 31:207, 1980.

Reber, H.A., Tweedie, J.H., Austin, J.L.: Pancreatic secretions as a clue to the presence of pancreatic cancer. Cancer 47(6):1646, 1981.

Tweedie, J.H., Mosley, J.G., Austin, J.L., Reber, H.A.: Effect of 16, 16 dimethyl prostaglandin E₂ on aspirin-induced permeability changes in the pancreatic duct. Am. J. Surg. 141:22, 1981.

Doria, J.C., Mosley, J.G., Reber, H.A.: Effect of a single exposure to a carcinogen on pancreatic function in hamsters. J. Surg. Research 30:21, 1981.

Reber, H.A., Tweedie, J.H., Austin, J.L., Maslin, S.C.: Pancreatic cancer: Diagnostic value of pancreatic function tests. Cancer Detection and Prevention, in press.

From 06/01/80 to 05/31/83

FY 81: \$244,016

Dr. Avery D. Weisman, Massachusetts General Hospital, Boston,
Massachusetts 02114

Objectives: For the Total Project: (1) To examine the circumstances, personality style, and psychosocial consequences of patients with a recent recurrence of cancer; (2) to compare the effects of recurrence with the impact and implications of having a newly diagnosed cancer, based on a previous study; (3) to compare the accuracy of a screening instrument in detecting patients who are at greatest risk for increased emotional distress and impaired coping; (4) to investigate the most important personal and emotional variables in assessing future psychosocial difficulties; and (5) to examine and compare effectiveness of two different psychological methods for relieving distress and improving how patients cope with diagnosis and recurrence of cancer.

For the Current Year: (1) To establish a referral network for identifying patients with a recent recurrence at the designated sites and who fulfill other criteria; (2) to develop and refine assessment procedures beyond those already used in a previous project, while preserving comparable parameters; and (3) to modify intervention methods in accordance with the requirements of recurring patients.

Accomplishments: Data collection began in September, 1980, after developing appropriate assessment procedures. By the end of the current (01) year, we will have studied, intervened with or followed at least 50 patients. One-third of these are followed without explicit intervention; the other two-thirds will receive short-term interventions. Because patients will be taken into the project during 02 year, complete follow-ups will be available on only the early patients. While numbers are still too small to permit reliable analysis, it seems that levels of distress at recurrence are not as high as originally anticipated. Nevertheless, the refusal rate (15%) is about the same as that found with newly diagnosed patients at the same sites.

Early results confirmed that the strategy for obtaining larger numbers of patients needed change from that with newly diagnosed patients. Unless a recurrent patient is very ill, he is treated as an outpatient, and a considerable time elapses before preliminary studies lead to confirmation of the diagnosis. By this time, the patient may have returned to his home community, to be followed by his local physician in a community hospital or office.

Comparing the level of distress and effectiveness of how patients cope with respect to newly diagnosed and newly recurrent patients will help to decide an important question of when preventive intervention is most useful, namely, at diagnosis or recurrence.

If it turns out that recurrent patients are no more distressed than newly diagnosed patients after intervention, it is reasonable to infer that

Program Director: Sandra M. Levy, Ph.D

treatment failure may not be as disruptive as sometimes thought, and that psychosocial issues are likely to be less intrusive as time goes on.

The possibility of further developing an accurate screening instrument for finding patients at higher emotional risk after recurrence has the same magnitude as finding similar patients at diagnosis. This will mean that personality studies can focus on more vulnerable patients, using specific dependent variables, instead of simply adding further descriptive data.

Intervention methods which are designed to detect and help patients cope with identifiable, cancer-related problems will also be cost-effective in confining major efforts to that cancer population at greater risk.

Plans: (1) To access more patients fitting pre-selected criteria: (2) to offer psychosocial interventions to two-thirds of these patients, and following at two-month intervals for six months; (3) to examine differences between recurrent patients and newly diagnosed patients who refuse intervention, and to determine which period entailed more distress for all patients interviewed; and (4) to seek out patients from earlier work who either recur or seem to be in indefinite remission, and to re-evaluate them in the light of recent events.

Publications:

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Grant 27092: Factors in Self-Help Smoking Cessation Attempts

From 03/01/81 to 02/28/82

FY 81: \$161,085

Richard H. Hart, M.D., Dr. P. H., Loma Linda University, Loma Linda,
California

Objectives: The vast majority of those who stop smoking do so on their own, without participation in a formal cessation program. The aim of this study is to identify psychosocial and environmental factors which are related to both successful and unsuccessful non-formalized attempts at smoking cessation. Impact of specific techniques on success in smoking cessation will be examined. Three groups of particular interest, as well as members of the general population, will be included in the study. These are health conscious individuals who present themselves at community screening programs, heavy users of alcohol from an outpatient alcohol-abuse treatment program and VA outpatients, including many older male smokers at high risk for smoking-related disease.

Plans: Data gathered during previous contacts with each of the study groups will be coded. A sample of each study group will be personally interviewed. A pre-coded questionnaire will be developed from these interviews and the literature, and mailed to each subject. Data will be analyzed for each study group and pooled if appropriate.

Program Director: Catherine S. Bell, M.S.

Grant 27112: Cancer Risk Among Women Exposed To DES In Pregnancy

From 01/01/81 to 12/31/81

FY 81: \$378,995

Dr. E. Robert Greenberg, Dartmouth Medical School, Hanover, New Hampshire
03755

Objectives: This project is an historical cohort study being conducted at three study centers with a central facility for data coordination. The objectives are (1) to quantify relative and attributable incidence rates of breast and gynecologic cancers, benign breast disease, and total mortality for women exposed to DES during pregnancy; (2) to identify and adjust for relevant confounding variables in estimating the breast cancer risk for DES exposure (variables include family history of breast cancer, menstrual history, parity, age at termination of first pregnancy, and other exogenous estrogen use); (3) to describe the pathologic features of any tumors associated with DES use; and (4) to describe the occurrence of cancers other than breast or gynecologic in the exposed and unexposed groups.

Accomplishments: The first year of this three-year project was primarily a time for planning, for solidifying collaborative arrangements and for obtaining preliminary information from the medical records of exposed and unexposed women.

A protocol and manual of procedures outlining the objectives and providing guidelines for study conduct to insure methodologic standardization have been written and distributed to the study centers.

The questionnaire, which will be mailed to each subject (or her next of kin), has been designed and pilot tested at the study centers. It has been approved by each institution's human subjects review board and is ready for use in the field, as are additional forms for data collection.

The pilot test of study instruments and methods yielded a high response rate (91%). This would indicate that the approach to the tracing and contacting of the cohort is a feasible way of obtaining the information needed to evaluate the hypotheses under investigation. Furthermore, the planned cross-validation check between questionnaire responses and information available on a subject's medical record is to be used as a confirmatory mechanism and to lend support to the validity of the questionnaire.

Tracing has begun at each study center. Women have been traced via telephone directories, city directories, motor vehicle registrations, searches of vital records, and inquiries of all sources of information likely to provide a lead in locating a woman. To date, approximately 1,500 women have been traced.

Computer programs are currently in use at the Dartmouth Coordinating Center for the entry and verification of data, quality checks, and the generation of monthly reports. The data base is continually being updated and checked for errors and inconsistencies. Programs for performing preliminary analysis have been developed and cross tabulations on data from the three centers have been run.

Program Director: Robert T. Bowser, Ph.D.

Plans: We are now entering the major data collection phase of this study.

Women will be sent a letter explaining the study and requesting their participation. Along with the letter, they will receive a questionnaire to complete and return. Every effort will be made to obtain the information requested on the questionnaire from each study subject or her next of kin.

For those women who have suffered one of the outcomes under investigation, additional information will be sought from medical record sources. Pathology reports and slides of all cases of breast cancer will be requested and reviewed using a uniform protocol.

Work on data processing will continue as will preliminary runs to test procedures for data format and output. Automated methods for quality control and validity checking will be further developed. Work to determine the optimal method for data analyses will continue along with efforts to investigate the utility of existing programs for performing these analyses. The bulk of the work in data analyses will be performed in the third year.

From: 03/01/80 to 05/25/81

FY 81: 0

Mr. Anthony Sardinas, State Department of Health Services, Hartford, Connecticut 06115

Objectives: A prototype study was that of the University of Chicago which examined male offspring exposed in utero to diethylstilbestrol, and which reported an excess of abnormalities in the external genital tract. Using that study as a point of departure and following some of the guideposts established by the DES Task Force Summary Report, for determining the incidence of testicular hypoplasia, cryptorchidism, and the risk of testicular cancer, the plans were laid for the initiation of this case-control study. This study will be designed to answer the question of whether there is an increased risk of testicular cancer among men exposed to DES in utero. If an increased risk of cancer is suggested, then a surveillance system would be initiated in order that those exposed might undergo further evaluation to ascertain if these abnormalities are associated with DES exposure. At the same time, the results will be used to guide public health and private physician screening so that detection procedures, if warranted, might be developed and implemented promptly.

Accomplishments: We have identified 173 cases of primary cancer of the testes, which have histological confirmation and reported to the Connecticut Tumor Registry (CTR) between 1945 and 1980. Only individuals born between 1945 and 1972 are eligible for the study. One hundred and fifty-three birth certificate controls have been matched by: (1) birthdate (same year of birth); (2) race; (3) maternal age + years; and (4) attending physician. The remaining twenty birth certificate controls will be selected by June 1, 1981. Birth certificate controls are subjected to both a City Directory search and Motor Vehicle linkage to confirm Connecticut residency up to the date of diagnosis for the matched testicular cancer case. The selection of seventy-three subjects for the second control group for Connecticut-born patients admitted to the medical service of a hospital has also been completed. Another 41 hospital controls will be selected by July 1, 1981. Forty cases will not have hospital controls due to uncooperative hospitals. Letters have been sent to 144 obstetricians to request permission to review medical records for this study.

Plans: Obstetricians will be approached by telephone and asked to provide additional medical records for this study. The obstetricians' records for prenatal history will be reviewed for cases, birth certificate controls, and hospital controls. The method of case-control analysis for maternal pairs will be used. The analysis will be patterned after the studies of Mantel and Haenszel (1959) who derived a general method of analysis that can be supplied even when the number of controls varies from one case to another. The test of statistical significance and odds ratio will also be calculated.

Program Director: Robert T. Bowser, Ph.D.

Grant 27279: Cancer Control and Community Physicians

From 04/01/80 to 03/31/83

FY 81: \$199,432

Dr. Wesley Fowler, University of North Carolina, School of Medicine
Chapel Hill, North Carolina 27514

Objectives: The objective of this project is to improve the clinical management of cancer patients in North Carolina. To accomplish this objective, the project combines basic research into the patterns of care provided by physicians in different type practice settings for selected disease sites (breast, endometrial and cervical) and the use of that data to encourage the acceptance of current technology in the clinical care provided cancer patients. The project is considered a demonstration cancer control effort and will provide the empirical basis for the development of a cancer control program involving community-based physicians in a predominantly rural southern state. The data derived from this study should add to the growing technology transfer literature as applied to cancer control by identifying problems in the transfer of up-to-date detection and treatment methods and the causes of such problems.

Accomplishments: Arrangements were completed in each of the three study sites and the two control sites for the conducting of the medical chart review. Sample sets of criteria for the diagnosis, pretreatment evaluation and treatment of breast, cervical and endometrial cancer were compiled from several existing criteria lists. These were supplied to a steering committee at each of the study hospitals for their review and revision. A different version for each hospital was then distributed to all the physicians diagnosing and/or treating those patients. The comments from that review were incorporated into final criteria for each study site. Data collection forms were designed and pretested and then used in a chart review of all breast, cervical and endometrial cancer patients treated in all five hospitals from January 1977 through December 1980. The data collected was then compared to the criteria for that hospital.

Plans: The further steps are: (1) preparing descriptive comparisons of performance as measured through the chart review to the criteria; (2) using these as feedback to the physicians on their individual performance; (3) conducting an audit of medical records of patients treated after the feedback to detect any feedback effects; and (4) planning continuing education programs.

Program Director: Donald N. Buell, M.D.

Grant 27281: Social Epidemiology of Cancer Care

From 05/01/80 to 04/30/83 FY 81: \$116,201
Dr. Anita M. Francis, Fred Hutchinson Cancer Research Center, 1124
Columbia Street, Seattle, Washington 98104

Objectives: The objective of this study is to describe the behavioral determinants of state of disease at diagnosis and the patterns of care received (type, timing, and number of services used) for newly diagnosed colorectal cancer patients residing in a defined population area (King County, Washington). The design of the study calls for interviews of patients and use of data from the central tumor registry (The Cancer Surveillance System at the Fred Hutchinson Cancer Research Center). This study will provide useful information for the planning of health services, determination of health manpower requirements and the planning of health care professional education.

Accomplishments: Project starting date was May 1, 1980. Pilot testing of the instrument was conducted October 1 through November 30, 1980, following activation of the accrual process and contact with local area physicians. As of March 31, 1981, 111 interviews have been completed. Permission has been obtained to include members of the Group Health Cooperative of Puget Sound. This will increase the generalizability of the results and will permit a comparison of patterns of care for a prepaid versus a fee-for-service provider system. Currently a data management base is being created to allow maximum efficiency and flexibility in data processing. Some preliminary analyses on the first 100 cases will begin as soon as this procedure is complete.

Plans: Plans call for a continuation of the data collection and computer preparation phases and the beginning of the preliminary analyses during the second grant year. Generally, this research will enable discussion of the issue of patient delay in arriving at a cancer diagnosis and the factors which cause this delay--symptom characteristics, patient characteristics, physician and system characteristics. It will also enable examination of such topics as access, continuity, and satisfaction with care.

Program Director: Rosemary Yancik, Ph.D.

Grant 27328: Effect of Tumors on Eustachian Tube and Hearing

From 05/01/80 to 10/31/82

FY 81: \$38,695

Dr. Eugene N. Myers, Eye and Ear Hospital, 230 Lothrop Street,
Pittsburgh, Pennsylvania 15213

Objectives:

1. Assess middle ear and hearing function pre and post treatment for tumors of the head and neck.
2. Develop guidelines to reduce potential hearing loss from head and neck cancer treatment.

Accomplishments: Patients are now being accrued into the study. The initial study suggests that patients with operations on the maxillary sinus or extensive operations involving the soft palate and the muscles attached to the Eustachian tube, do indeed, produce a transient middle ear effusion. We will continue to accrue and study the new patients into this, and continue to study the patients already accrued longitudinally.

Program Director: Harry Handelsman, D.O.

Grant 27332: The Self-Help Process in Smoking Cessation

From 05/01/80 to 07/31/83

FY 81: \$136,877

Dr. S. Leonard Syme, Institutes of Medical Sciences, San Francisco,
California 94115

Objectives: This is a proposal to describe the characteristics of smokers who quit on their own as compared to (a) smokers who quit in formal, organized groups, (b) smokers who have tried unsuccessfully to quit, and (c) smokers who have never tried to quit. The initial goal is to formulate a comprehensive model of the smoking cessation process and to describe characteristics related to that process. The final goal is to assess the potential value of this model for the design of future smoking control programs.

Accomplishments: During our first year, we conducted a series of pilot open-ended interviews with all three types of smokers. In these interviews, we questioned respondents about their smoking histories and about their attempts to quit smoking. Three judges independently reviewed the tapes to pick out key items relevant to the smoking cessation process. Five distinct stages were identified. The reports of the judges were used to formulate four questionnaires--one for each of our study groups. We have conducted two pretests of this questionnaire and it is now printed and ready for administration. The questionnaire has approximately 100 items and takes one and one-quarter hours to complete. The items on these questionnaires are objective and easily codable. Questions relate to the social and demographic milieu of the four groups, the attitudes and beliefs they hold about smoking, feelings in relation to smoking, procedures and techniques used in quitting smoking, and events associated with quitting and returning to cigarettes. A self-administered questionnaire also has been developed to obtain information on general health status and personality factors. This questionnaire will be left with the respondent for mailing to us after the interview. We have now identified a number of companies who can provide us with respondents and are beginning recruitment efforts to identify 640 eligible study subjects.

Plans: Our plans for the second year are to continue recruitment efforts and to complete 640 interviews. We have employed interviewers and will soon begin a training program for them. During the second year, we will begin, on an ongoing basis, to edit, code and reduce data from these interviews.

Program Director: Catherine S. Bell, M.S.

Grant CA 27338: Nuclear Antigens in Human Colorectal Cancer

From: 09/01/79 to 05/31/82

FY 81: \$90,622

Dr. Lubomir S. Hnilica, Vanderbilt University School of Medicine, Station 17,
Nashville, TN 37232

Objectives: Our principal objective is the development of useful immunodiagnostic reagents as markers for malignant transformation and for the development of malignant and pre-malignant lesions in cells of human large bowel. To achieve this objective we investigate systematically nuclear and nucleolar protein antigens in cultured human colon carcinoma cells, human colon adenocarcinoma transplanted in hamsters and in normal or hyperplastic human colonic tissues. We hope to identify specific antigens with the process of carcinogenesis and to develop objective immunological assays to identify cells committed to malignancy. Special emphasis will be placed on detailed investigation and characterization of cell-specific complexes of chromosomal nonhistone proteins with DNA and their correlation to carcinogen-modified DNA sites.

Accomplishments: One of our most significant accomplishments is the development of the method for rapid detection of antigenic proteins separated by polyacrylamide gel electrophoresis. The electrophoretically separated proteins are transferred to nitrocellulose sheets. After incubation with an appropriate antiserum the reactive protein antigens are detected by staining with peroxidase-antiperoxidase. This method permits a rapid survey of antisera specificity with a large number of cellular extracts or purified antigen preparations. Nonspecific staining can be removed by immuno-absorption making this method for rapid antigen detection highly selective.

Using this method we have found antisera to human colon cancer cell lines HT29 and LoVo to react with many protein bands in HT29, LoVo or human colon adenocarcinoma chromatin. Major bands were in the molecular weight (m.w.) range of 62-73K as well as 63K, 89K, and 98K. When the antisera were immuno-absorbed with normal human colon chromatin almost all stained bands were removed. Two principal polypeptides (m.w. 69K and 98K) were not found in normal human colon, placenta, or other tissues. It was concluded that the 69K and 98K antigens are specific for human colon carcinoma. Another line of human colorectal carcinoma maintained in hamsters (GW39 tumor) did not contain these two antigens. Moreover, chromatin of the GW39 tumor did not react by complement fixation with the HT29 or LoVo antisera and vice versa, antisera to GW39 dehistonized chromatin were not reactive with LoVo or HT29 chromatin. We find this phenomenon potentially significant for studies on immunological interactions between the tumor and its host.

Plans: Using the immunotransfer method developed in our laboratory, we wish to explain the dramatic immunological differences between the chromatin of the LoVo or HT29 cell lines and the GW39 transplantable carcinoma, to isolate and characterize the specific chromosomal non-histone 68K and 98K antigens and to investigate their significance as immunological markers in large bowel carcinogenesis.

Publications: None.

Program Director: Vincent J. Cairoli, Ph.D.

From 09/01/79 to 06/30/82

FY 81: \$87,586

Dr. Vladimir Petrow, Department of Pharmacology, Duke University Medical Center, Durham, North Carolina 27710

Objectives: To identify a steroid for adjunctive treatment of androgen dependent prostatic carcinoma which will act by irreversibly inhibiting the enzyme 5α -reductase by k_{cat} type of mechanism. Longer term, attention will be directed to improving the uptake of the inhibitor by the prostate in order to enhance target-organ specificity.

Accomplishments: The first part of this project may now be regarded as brought to a successful conclusion. Employing an in vitro assay for rat prostatic 5α -reductase, a number of steroids have been synthesised and examined for enzyme-inhibiting activity. A 4-pregnene-3,20-dione has been identified which equals progesterone in enzyme-inhibiting potency. Interestingly, it only functions as an inhibitor in the presence of NADPH. Tissue-culture studies using human BPH preparations confirm its activity as an enzyme inhibitor in this biochemical model (with A. Sandberg). Kinetic studies are in agreement with the conclusion that the compound acts by a k_{cat} type of mechanism. Megestrol acetate, a related 4-pregnene-3,20-dione with palliative effects in prostatic cancer, has been found to be virtually devoid of 5α -reductase inhibiting activity. The thesis has been developed that our inhibitor + megestrol acetate forms a combination worthy of study. Part of this data was reported at the symposium on, "The Prostatic Cell: Structure and Function, March 5-7, 1981," held at Roswell Park Memorial Institute and sponsored by The National Prostatic Cancer Project.

Plans: We plan to develop a biochemical/biological profile of our inhibitor with particular attention directed to its in vivo activity. Chemical work will continue to provide a supportive function.

Publications:

Petrow, V., Wang, Y., Lack, L. and Sandberg, A., Prostatic Cancer. I. 6-Methylene-4-pregnene-3-ones as Irreversible Inhibitors of Rat Prostatic Δ^4 -3-Ketosteroid 5α -Reductase. Steroids, (In Press).

Petrow, V. and Lack, L., Studies on a 5α -Reductase Inhibitor and Their Therapeutic Implications. In The Prostatic Cell, (In Press).

Program Director: Andrew Chiarodo, Ph.D.

Grant 27376: Use of Self-Hypnosis for Control of Pain, Nausea, and Vomiting in Adolescents with Cancer

From 09/30/79 to 07/31/82

FY 81: \$195,484

Dr. L. Zeltzer, The University of Texas Health Science Center, 7703

Floyd Curl Drive, San Antonio, Texas 78284

Objectives: The objectives of this study in adolescents with cancer are:

- (1) to evaluate the effectiveness of hypnosis for reduction of pain, anxiety, and vomiting in older children and adolescents with cancer; (2) to compare the effects of hypnosis with non-hypnotic behavioral support; (3) to evaluate the effects of behavioral intervention on chronic anxiety, self-esteem, impact of illness, and feelings of responsibility for health; (4) to evaluate the role of patient suggestibility in response to hypnosis; (5) to evaluate the extent to which observers can reliably assess acute pain and anxiety in adolescents; and (6) to identify patient and family stresses associated with the treatment of childhood cancer and to identify factors that help families cope.

Accomplishments: Forty-one patients have been entered into the study, with 10 in a non-intervention category. The protocol has been altered from its original design so that patients in the support group will receive hypnosis intervention after two to three procedures or courses of chemotherapy. Preliminary analysis of the four psychological tests given during baseline and again at six months after intervention (n=15) showed decreased trait anxiety and increased self-esteem for both the support and hypnosis groups (p .01). There were no significant changes on the impact of illness scores or the health locus of control test. Analysis of the patient self-reports during baseline and intervention for anxiety and discomfort during medical procedures found a significant reduction for both anxiety and discomfort in the hypnosis group (p .0001), but no significant reduction in either symptom for the support group. Also, the interrater reliability for 210 patient and observer ratings of medical procedures was .71 for anxiety and .60 for discomfort (Pearson's r, both p .0001), indicating that an observer can rate a patient's discomfort and anxiety during procedures with some degree of reliability. The testing of patient suggestibility and the family assessment section of the study are continuing. Additionally, most procedures are being videotaped and catalogued.

Plans: The plans for the coming year: (1) to enter into the study as many adolescents as we can follow and terminate with enough time to allow for data analysis; (2) to begin a limited substudy of hypnosis for procedures and chemotherapy in children ages 7-10 years; (3) to complete the family assessment, paying special attention to the family's role in helping children cope with pain and anxiety; (4) to analyze our data, not only as described initially, but also in terms of age, cultural orientation, and patient suggestibility; and (5) to edit and catalogue our series of videotapes so they can be used for teaching.

Program Director: Sandra M. Levy, Ph.D.

Grant 27378: Environmental and Occupational Cancer Mortality Estimation

From 09/01/80 to 08/31/81

FY 81: 0

Dr. Michael J. Symons, University of North Carolina, Chapel Hill, North Carolina

Objectives: The proposed research will develop and apply different approaches for estimating environmental and occupational contributions to cancer mortality among U.S. whites.

Accomplishments:

- A. A statistical basis for the differencing of age and site-specific cancer rates for white males and white females has been investigated and submitted for publication review. This will be utilized in calculating the proportion of cancers that may be attributable to occupational effects.
2. A computer program has been prepared for the calculations involved in the approximation of the fraction of cancer attributable to occupational effects.
3. Programs for the cluster analysis approach in approximating the proportion of cancers that may be environmentally related have been adapted for use at UNC computer facilities.

Plans:

1. Data acquisition from EPA at Research Triangle Park in North Carolina will be completed this spring in preparation for analyses during the summer.
2. Write-up of results and subsequent analyses will be performed from September to December 1981.

Program Director: Jan M. Howard, Ph.D.

From 05/01/79 to 04/30/83

FY 81: \$91,162

Dr. Joseph R. Drago, Department of Surgery, Division of Urology, The Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033

Objectives: During the last few years, this laboratory unit has identified as the single most effective agents in treating the Nb rat prostate adenocarcinoma tumors as being, cyclophosphamide and cis-platinum. Secondly during the last 18 months, we have tried to evaluate combination therapies of combination of two chemotherapeutic agents, best combinations thus far have been cis-platinum and cyclophosphamide with adriamycin and cyclophosphamide being the second most active combination. During the last 12 to 14 months, we have evaluated triple drug therapy mainly in two different combinations, that is cis-platinum, adriamycin and cyclophosphamide, and BCNU, 5-FU, and adriamycin. The former has been most efficacious in reducing final tumor volume, decreasing the number of metastasis, and leading to the largest number of animals in each experiment with complete tumor regression. Finally, we are evaluating the use of combination chemotherapy and hormonal manipulation in the androgen sensitive tumor line and this has resulted in the following; early castration and cyclophosphamide has been more effective than either treatment alone in reducing final tumor volume, metastasis and increasing the number of animals with complete tumor regression. However, a more dramatic effect has been seen with the use of castration and early triple drug (cis-platinum, adriamycin and cyclophosphamide) treatment when one considers the same parameters.

Accomplishments: During the last year, we have initiated collaborative experiments regarding e.m. characterization of these tumors with Dr. Irwin Leav D.V.M., and Dr. Frederick Merk, Ph.D. and Dr. Peter Onfer, Ph.D. at Tufts University. Preliminary data has suggested that there are striking differences between the androgen sensitive and androgen insensitive tumors of the Nb rat prostatic adenocarcinoma model. Furthermore, there are similarities with respect to testosterone metabolism in each of the respected tumor types, (androgen sensitive and androgen insensitive). In addition to the chemotherapeutic experiments described in the objectives above, where continues on the determining of the best single, and combination chemotherapies for the androgen insensitive tumors, as well as illucidation of other combination treatments, such as, hormonal therapy and combination chemotherapy in the androgen insensitive tumor. This year we are continuing to evaluate these various chemotherapeutic and hormonal combinations as well as evaluating direct effect of hormonal manipulation on the tumors, i.e. treating androgen sensitive tumors with direct administration of estrogen to the tumor bed as well as administration of estrogen via these silastic implants.

Major Research Fundings: 1. National Prostatic Cancer Project Grant 27380

Lectures:

1. American Urologic Association, Poster Session (2) regarding Nb Rat Prostatic Tumor, 1980
2. Mid-Atlantic Section AUA, (2) Papers, regarding combination chemotherapy and hormonal manipulation in this tumor, 1980

Program Director: Andrew Chiarodo, Ph.D.

3. Society of University Surgeons, Nb Rat Prostatic Carcinoma Model discussed, 1980
4. Academic Association of Surgeons, talk on Combination Chemotherapies, 1980

In addition, our work with hormonal induction is completing the preliminary phase in which we have induced a number of tumors in a period of time, varying from 26 to 36 weeks initial characterization and determination of varying tumor characteristics had begun.

Plans: During the next 12 months, we plan to continue to try to correlate effects of various chemotherapeutic and combination therapies in this model system. In addition, we will continue our work with receptors to determine if there are any correlations that can be drawn with receptor counts and predicting appropriate chemotherapies. Finally we will continue to pursue our collaboration with Tufts University in elucidating the electron microscopy characteristics of these tumors.

From 12/01/79 to 06/30/83

FY 81: \$30,685

Dr. G. Elizabeth Mobbs, Department of Surgery, University of Toronto Medical Sciences Building, Toronto, Canada M5S 1A8

Objectives: The concentration of steroid hormone receptor proteins in normal target organs has been found to be related to the degree of hormonal sensitivity, and the subcellular distribution of these proteins is dependent on the hormonal status of the subject. These relationships may be upset in neoplastic disease. The aim of this study is to characterize fully an accurate and sensitive assay for nuclear androgen receptor (AR) in human prostatic tissue, and to examine the relationships between cytosol and nuclear AR, the histopathology of the tissue, the endocrine status, and the course of the disease in patients with prostatic carcinoma. This will increase our understanding of the mechanisms controlling this disease, and may assist in the selection of therapy.

Accomplishments: We have found that absorption of nuclear AR by hydroxylapatite after incubation of KCl nuclear extract with radioactively labelled ligand results in a highly sensitive and accurate assay. Preliminary data from prostatic specimens suggests that, although the concentration of total cytosol AR is very variable, especially in prostatic carcinoma, the concentration of KCl-extractable nuclear AR appears to be related to the concentration of cytosol AR which was occupied in vivo by endogenous androgens. We have found that this relationship also holds in the rat ventral prostate, which is used as a model androgen-sensitive tissue. During the next few months, we expect to accumulate data on a further 30 human specimens, and will determine whether the relationship between cytosol and nuclear AR is identical for all types of tissue, or whether it is modified by the histopathology. Further work on the animal model will demonstrate whether or not the in vitro results are representative of in vivo physiological events.

In the animal model, we shall also investigate whether a secondary rise in cytosol AR concentration which has been observed after castration is accompanied by a rise in nuclear AR. This secondary rise might correspond to the high concentrations of cytosol AR observed in tissue from some androgen-deprived patients, some of which appears to be translocated into the nucleus.

Plans: It is planned to integrate the biochemical data on the human tissue with the histopathology and the course of disease, including the clinical response to hormonal manipulative therapy. It may be possible to establish a "threshold" concentration for nuclear AR, below which androgen sensitivity is lost.

Publications: Mobbs, E.G., Johnson, I.E. and Connolly, J.G. Role of Cytosol Androgen Receptor in Determining Androgen Binding by Prostatic Nuclei. Abstract, 63rd Annual Meeting of the Endocrine Society, 1981. (In press).

Program Director: Andrew Chiarodo, Ph.D.

From 09/30/79 to 05/31/82

FY 81: \$123,986

Dr. Leland W. K. Chung, Pharmacology, Box 297, University of Colorado,
Boulder, Colorado 80309

Objectives: The influence of developmental mechanisms on latent prostatic cancer development are studied in depth. Two models are used in this study. One, Nb rat treated with either testosterone or estradiol alone or in combination were examined at various developmental periods for possible prostatic cancer formation. Tissues were examined by histological and biochemical means. Potential sensitive histochemical and biochemical methods for monitoring the progression of prostatic cancer development in this hormone-induced Nb model will be investigated. In addition, possible interaction between sex steroids and other promoters in the present system will also be assessed. Two, a cell interaction model utilizing urogenital sinus mesenchyme (UGM) as an inductor and the directive induction of bladder epithelium to form prostate will be monitored. The respective biochemical characters of epithelium and stroma will be defined. Since cell interaction occurs between species and across organs, the possible inductive influences in heterorecombinants containing normal and neoplastic human tissues and mouse UGM are currently under investigation.

Accomplishments: We have found several useful biochemical markers for monitoring the progression of prostatic cancer development. We have also examined the biological potential of embryonic stroma in inducing prostatic phenotypic expressions. These findings were reported recently at meetings of the Prostatic Cancer Project and Western Pharmacology Society. Manuscripts (see publication list) are either published or will appear later in various scientific journals.

Plans: Our research thrust will be placed on (1) interactions between sex steroids and promoters in prostatic cancer development. The biochemical characteristics of stroma and epithelium will be defined with particular emphasis on relationship of sex steroids and dorsolateral prostatic cancer development. (2) Heterotypic recombinants involving tissue interactions between species will be studied in depth. The possible reversal of prostatic cancer phenotypes by embryonic tissues will be tested.

Publications:

Chung, L.W.K., Thompson, T.C., and Breitweiser, K. Sensitive Biochemical Methods to Distinguish Hormone-Dependent and Independent Dunning Tumors of Prostatic Origin. Proc. West. Pharmacol. Soc. 24, 1981.

Neubauer, B.L., Anderson, N.G., Cunha, G.R., Towell, J.F. and Chung, L.W.K. A New Isocratic HPLC System for the Measurement of In Vitro Testosterone Metabolism in Tissue Recombinants Composed of Adult Mouse Urinary Bladder Epithelium and Urogenital Sinus Mesenchyme. Proc. West. Pharmacol. Soc. 24, 1981.

Program Director: Andrew Chiarodo, Ph.D.

Chung, L.W.K., Anderson, N.G., Neubauer, B.L., Cunha, G.R., Thompson, T.C. and Rocco, A.K. Tissue Interactions in Prostate Development: Roles of Sex Steroids. In: The Prostatic Cell: Structure and Function. (G. P. Murphy, Ed.) Alan R. Liss, Inc., N.Y., 1981 (In Press).

Thompson, T.C. and Chung, L.W.K. Detection of Normal Levels of Androgen Receptor in the Kidney Cytosol of Testicular Feminized (Tfm/y) Mice: Effect of Sodium Molybdate. Fed. Proc. 40, 1981.

Anderson, N.G., Rocco, A.K. and Chung, L.W.K. Progression of Prostatic Adenocarcinoma in Nb Rats. J. Supramol. Structure and Cell. Biochem. Suppl. 5: 223. 1981.

Breitweiser, K., Butley, M.S., Malkinson, A.M. and Chung, L.W.K. Photo-affinity Labeling Differences Between Hormone-dependent and Independent Prostatic Adenocarcinoma Cells to 8-azido-cAMP. Cancer Research (Submitted)

Neubauer, B.L., Anderson, N.G., Cunha, G.R., Towell, J.F. and Chung, L.W.K. Testosterone Metabolism in Host Prostate, Host Bladder and Tissue Recombinants Composed of Adult Urinary Bladder Epithelium and Urogenital Sinus Mesenchyme. Steroid. (Submitted).

Cunha, G.R., Shannon, J.M., Neubauer, B.L., Sawyer, L.M., Fujii, H., Taguchi, O. and Chung, L.W.K. Mesenchyme-epithelial Interactions in Sex Differentiations. Human Genetics, 1981 (In Press).

Cunha, G.R. and Chung, L.W.K. Stromal-epithelial interaction: I. Introductions of Prostatic Phenotype in Urothelium of Testicular Feminized (Tfm/y) Mice. J. Steroid Biochem. (Submitted).

Neubauer, B.L., Chung, L.W.K., McCormick, K., Shannon, J.M. and Cunha, G.R. Epithelial-mesenchymal Interactions in Prostatic Development. II. Biochemical Observations of Prostatic Induction by Urogenital Sinus Mesenchyme in Epithelium of the Adult Mouse Urinary Bladder J. Cell. Biol. (Submitted).

From: 07/01/79 to 04/30/82

FY 81: \$130,027

Dr. Bertram I. Cohen, Veterans Administration Hospital, First Avenue at East 24th Street, New York, New York 10010

Objectives: Our studies are designed to test: 1) the effects of induced changes of the colonic concentrations of sterols, bile acids, and their metabolites on large bowel cancer induced by chemical carcinogens. These studies will show whether primary bile acids, secondary bile acids and/or cholesterol have tumor promoting properties in our animal model for colon cancer; 2) whether plant sterols inhibit or retard large bowel carcinogenesis in animals and in man. These studies using the sterol β -sitosterol, are designed to show whether a component normally present in increased amounts in vegetarian diets can affect tumor formation and development; 3) whether sulfation of bile acids, particularly lithocholic acid, influences the ability of these compounds to promote large bowel cancer. These studies are designed to detect and identify bile acid sulfates in feces and determine whether different concentrations of these compounds are present in patients at risk for colon cancer; and, 4) whether certain cholesterol metabolites affect large bowel cancer. After identifying cholesterol sulfate in human feces, studies are underway to quantitate the amounts present in different populations.

Accomplishments: The effect of feeding 1% of β -sitosterol on tumor number and/or size in rats treated with N-methyl-N-nitrosourea (MNU), 8 mg in 4 equal doses at 36 weeks, showed no statistical difference in MNU vs. MNU- β -sitosterol; % animals with tumors, (49% vs. 60%); tumors/animal (.87 vs. 1.09); tumors/tumor bearing animal (1.80 vs. 1.82) or tumor size (.42 cm vs. .40 cm), respectively. Apparently, the protective effect of β -sitosterol does not prevent tumor formation or alter tumor size. The tumor inhibiting potential of β -sitosterol (0.2%) in a rat model of colon cancer fed a semi-synthetic diet has been studied. The MNU group had a tumor incidence of 62% (0.86 tumors/animal, 1.39 tumors/tumor bearing animal) compared to the MNU- β -sitosterol group where there was a slight, but not significant reduction in the % animals with tumors (50%, 0.75 tumors/animal, 1.50 tumors/tumor bearing animal). The number of animals with tumors is suggestive of the tumor inhibiting potential of β -sitosterol in this model. This experiment shows that semi-synthetic diet + MNU causes a higher incidence in our model than MNU + a natural chow diet.

Plans: Experiments are planned to study the effects of MNU-induced colon tumors in rats fed a semi-synthetic diet supplement with: 1) deoxycholic acid (0.2%); 2) deoxycholic acid + cholesterol (0.2%) and, 3) deoxycholic acid + β -sitosterol, and to study the effects of intrarectal bile acid instillation on colo-rectal cancer using the N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) animal model (8 mg/rat) and lithocholic acid (6 mg/week), isolithocholic acid (6 mg/week), and lithocholic acid 3-sulfate (6 mg/week). In addition, we hope to synthesize cholesterol sulfate and to evaluate its presence in patients with ulcerative colitis, Crohn's disease and colon cancer.

Publications:

Cohen, B.I. and Raicht, R.F.: Plant Sterols Protection - Role in Chemical Carcinogenesis. In Inhibition of Tumor Induction and Development, M.S. Zedeck and M. Lipkin, Eds. Plenum Publishing Corp., in press, 1981.

Program Director: Vincent J. Cairoli, Ph.D.

From 09/05/79 to 11/30/82

FY 81: \$0 (Ann. \$59,385)

Dr. John R. Warren, Department of Pathology, Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, Illinois 60611

Objectives: The cell periphery plays a central role in determining the biological behavior (uncontrolled growth, metastasis) of malignant tumors. The objectives of this project are to define cell periphery properties of rat pancreatic acinar carcinoma cells, to delineate differences between cell periphery properties of neoplastic and normal acinar cells, and to relate cell periphery properties to growth characteristics of the acinar carcinoma. The cell periphery of both neoplastic and normal acinar cells is being examined by: (1) stimulation of protein secretion by cholinergic and peptide agonists which act by plasma membrane receptor-dependent mechanisms and by pharmacological agents which act by plasma membrane receptor-independent mechanisms; (2) binding of lectins to plasma membrane glycoproteins/glycolipids. In the final phase of this project, an attempt will be made with maturational agents (bromodeoxyuridine, retinoic acid derivatives) to revert the cell periphery properties of acinar carcinoma cells to normal and to examine the effects of such reversion (if observed) on growth of the carcinoma.

Accomplishments: Fragments obtained by simple mechanical disruption of the pancreatic acinar carcinoma demonstrated linear rates of protein and DNA synthesis when incubated for up to 5 hr in vitro. Continuous incubation of the fragments with [^3H]-leucine for 60 min resulted in labeling of rough endoplasmic reticulum, Golgi cisternae, and mature zymogen granules, revealed by electron microscope autoradiography. This result indicates transport of newly-synthesized protein from the rough endoplasmic reticulum to mature zymogen granules in approximately 60 min. The fragments were thus utilized as an in vitro system for determining the secretory competence of the pancreatic acinar carcinoma. Carcinoma fragments, pulse-chase labeled with [^3H]-leucine, responded to the agonist carbamylcholine by increased secretion of [^3H]-leucine labeled protein into external buffer medium. Secretion of labeled protein by the carcinoma fragments increased in concentration-dependent fashion between 10^{-8} to 10^{-5} M carbamylcholine, was completely inhibited at 40° , and was accompanied by an equivalent increase in the secretion of preformed amylase. A maximally effective carbamylcholine concentration of 10^{-5} M was observed for both carcinoma fragments and normal pancreatic lobules. However, the maximal rate of protein secretion by the carcinoma fragments was only approximately one-fifth the rate determined for normal pancreas lobules. Identical experiments utilizing the peptide secretagogue cholecystokinin-octapeptide revealed similar low rates of protein secretion by the carcinoma as compared to normal pancreas. However, stimulation of the acinar carcinoma fragments with the Ca^{++} ionophore A23187 resulted in rates of radioactive protein secretion equivalent to those observed for the normal pancreatic lobules. We tentatively propose that the secretory patterns demonstrated by the carcinoma fragments reflect defective stimulus-secretion coupling in the acinar carcinoma due to diminished numbers of membrane receptors for secretagogues and/or altered membrane receptor-dependent second messenger systems (Ca^{++} flux, altered cyclic nucleotide levels).

Program Director: William E. Straile, Ph.D.

Plans: Defective stimulus-secretion coupling reflects an important and definable difference between the cell periphery of neoplastic and normal acinar cells and will be completely defined by: (1) comprehensive comparison of neoplastic to normal cells using both secretagogues which act via plasma membrane receptors and via central effector mechanisms independently of plasma membrane receptors; (2) measurement of membrane-dependent "second messenger" systems, including changes in Ca^{++} flux and cyclic nucleotide levels (cAMP, cGMP); (3) quantitative determination of binding of radioactive secretagogue to acinar cell membranes. Experiments on the binding of ^{125}I -labeled concanavalin A have been completed and results are being analyzed to assess possible differences between neoplastic and normal acinar cells. Work utilizing other sugar-specific lectins (especially fucose- and sialic acid-specific lectins) is being initiated. The final phase of this project will assess actions of retinoic acid derivatives on secretory/lectin-binding properties and rates of cell proliferation in the acinar carcinoma. Other maturational agents will be assessed if deemed appropriate.

Publications:

Reddy, J.K., Rao, M.S., Warren, J.R., Qureshi, S.A., and Christensen, E.I.: Differentiation and DNA synthesis in pancreatic acinar carcinoma of rat. Cancer Research 40:3443-3454, 1980.

Warren, J.R. and Reddy, J.K.: Transplantable pancreatic acinar carcinoma. Cancer 47:1535-1542, 1981.

Warren, J.R.: Comparison of protein secretion by pancreatic acinar carcinoma and normal pancreas. Proceedings of the American Association for Cancer Research 22:138, 1981.

From 12/01/79 to 11/30/82

FY 81: \$122,776

Dr. Julius S. Horoszewicz, Department of Biological Resources, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, New York 14263

Objectives: Our objective is to delineate the utility of established in vitro human prostatic adenocarcinoma cells as a new model for studies on etiology, biology, detection and therapy of human prostatic adenocarcinoma cells as a new model for studies on etiology, biology, detection and therapy of human prostatic neoplasia. The subject of this study is the cell line LNCaP which we isolated from a metastatic lesion of human prostatic cancer. These cells are analysed as to their morphological characteristics and physiological properties when grown in cell culture systems. In addition, their malignant potential in nude mice and responsiveness to a variety of chemotherapeutic regimens and hormonal manipulation is studied. We expect to document that LNCaP cells grown in vitro or as tumors in nude mice, could be used as a source of human malignant prostatic tissue for morphological, endocrinological, biological, pharmacological and cell kinetics experiments and thus provide an alternative to the use of animal models in research on prostatic cancer.

Accomplishments: We have determined that LNCaP cells during growth in vitro for over three years have preserved epithelial morphology, maintain human male karyotype with marker chromosomes, could easily be cloned in soft agar, grow in a wide range of serum concentrations and continue to express macromolecules specific for human prostate such as human prostatic acid phosphatase (PAP) and human prostatic antigen (PA). Also, specific high affinity androgen and estrogen receptors were found in the cytosol. LNCaP cells injected into nude mice produce fast growing adenocarcinomas. These tumors contain high levels of antigenic markers (PAP and PA), which are also present in sera of tumor bearing animals. Chromosomal analysis of such tumors reveals a grossly aneuploid human male karyotype with several marker chromosomes. LNCaP tumor is hormonally responsive but is not totally dependent upon gonadal function. Significantly shorter latent periods, higher incidence of tumor development and larger tumor volumes were recorded in male versus female mice. Androgen, as well as 4S and 8S estrogen cytosol receptors were detected in tumors developing in mice of either sex. The pattern of inhibition of LNCaP tumor growth in nude mice treated with chemotherapeutic, antineoplastic agents indicates the probable use of this model in screening drugs for potential activity against human prostatic cancer. These findings were reported in two presentations at the Annual Meeting of the American Urological Association in May, 1981.

Plans: We plan to delineate in vitro the proliferative responses of LNCaP cells to several growth modulators such as hormones, growth factors and chemotherapeutic agents. We will also assess the homogeneity of LNCaP cells by analyzing properties of several single cell derived clones. The effect of hormonal manipulations on the frequency of tumor takes and the rate of tumor growth in nude mice will be measured. Comparison as to anti-tumor effectiveness of several chemotherapeutic agents against LNCaP tumor will be completed. In collaborative studies we will determine the value of labelled antibodies against prostate specific markers for the localization and/or detection of prostatic cancers grown in nude mice.

Program Director: Andrew Chiarodo, Ph.D.

Publications:

Horoszewicz, J.S., Leong, S.S., Chu, T.M., Kim, U., Chai, L.S., Kakati, S., Arya, S.K. and Sandberg, A.A.: In Murphy, G.P. (Ed.): Progress in Clinical and Biological Research : Models for Prostate Cancer. New York, Alan R. Liss, Inc., 1980, pp. 115-132.

Papsidero, L.D., Kuriyama, M., Wang, M.C., Horoszewicz, J., Leong, S.S., Valenzuela, L., Murphy, G.P. and Chu, T.M.: Prostate Antigen: A Marker for Human Epithelial Cells. J. Nat. Cancer Inst., 42:37-42, 1981.

Papsidero, L.D., Wojcieszyn, J.W., Horoszewicz, J.S., Leong, S.S., Murphy, G.P. and Chu, T.M.: Isolation of Prostatic Acid Phosphatase Binding Immunoglobulin G from Human Sera and its Potential for Use as a Tumor Localizing Reagent. Cancer Res., 40:3032-3035, 1980.

Grant 27555: Demonstration Project on Home Care Nursing for Cancer Patients

From 6/1/80 to 5/31/83

FY 81: \$207,096

Denise Oleske, R.N., M.P.H., Illinois Cancer Council, 36 South Wabash,
Suite 900, Chicago, Illinois 60603

Objectives: The Illinois Cancer Council and Illinois Department of Public Health are collaborating to improve regional community care for cancer patients by introducing the oncology nurse into the present system of home care, as teacher of public health nurses and regional consultant to home health care agencies. The effectiveness of the imposition of this particular specialist on the existing network of home care will be evaluated by the following methods, using study and control home health agencies: analyzing nursing interventions and select patient events vis-a-vis problems emerging from specific cancers, changing public health nurse knowledge resulting from interaction with the oncology nurse, and changing utilization patterns in home health care agencies. Positive results from this demonstration model might encourage budgeting for oncology nurses statewide to improve home care for the increasing numbers of cancer patients.

Accomplishments: I. Provide methods for improving cancer patient care by home health nurses and monitor their impact.

- A. Completed baseline measurements in a total of 39 home health agencies from two regions.
 - 1. Knowledge and attitude survey about cancer administered to 178 staff.
 - 2. Abstraction of data characterizing 788 cancer patient referrals in 1979.
- B. Introduction of interventions to improve care.
 - 1. Two Area-wide Oncology Nurse Coordinators (AONC) hired to provide education and patient consultation.
 - 2. Staffs from 20 home health agencies received 12 hours of continuing education.
 - 3. One hundred (110) cancer patients seen by AONC's.
- C. Monitoring of program impact.
 - 1. Abstraction of data characterizing cancer patient referrals from 1980 initiated.
 - 2. Nurse performance audit forms developed for: post-up and metastatic breast cancer, post-up and metastatic colon cancer, nutrition, and pain. Twenty-five audits have been completed in patients referred between January 1, 1981 and May 1, 1981.

Project Officer: Janet L. Lunceford, R.N., M.S.N.

3. Patient diaries were developed to measure medical care contacts; 18 have been completed.

II. Ensure community-based participation in the conduct of project activities.

- A. A Multidisciplinary Review Committee has been formed for each project region. Each is comprised of two physicians, two nurses, one social worker, and one lay person. Both Committees have met once.

Plans: 1. Continue referral data abstraction and monitoring of both nurses performance and select patient care events. Begin data analysis.

2. Deliver 18 hours of continuing education to staffs at participating agencies.

3. Increase number of patient contacts by AONC's.

Publications:

May, D., Oleske, D., et al. Role of the Oncology Nurse Coordinator in the community setting. Proc. 6th Ann. Congress, Oncology Nursing Society, 1981.

Oleske, D., Justo-Ober, P. et al. Survey of knowledge and attitudes about cancer among home health nurses. Proc. 6th Ann. Congress, Oncology Nursing Society, 1981.

Grant 27557: Environmental Cancer Prevention and Labor Health Education

From 04/01/80 to 03/31/83

FY 81: \$141,373 (Est.)

Dr. Virginia Wang, The Johns Hopkins University, 615 North Wolfe Street,
Room 3013, Baltimore, MD 21205

Objectives: The major objective of this project is the development, teaching, and evaluation of an occupational cancer health education curriculum to be incorporated into the instructional program of Empire State College's Northeast Regional Center (Albany) and Center for Labor Studies (New York City).

The majority of students served in this program are full-time union shop stewards and other union representatives from a wide variety of trades and industries. The unique composition of the student body will allow us to meet a second objective regarding the dissemination of awareness, resources, and knowledge to the great number of workers who are not enrolled in this or any other formal occupational cancer education program through contact of the course graduates with other workers at the worksite and in worker and community organizations. Further, we intend to disseminate the results of our development, implementation and evaluation efforts as a model of worker education with application to other learning institutions and appropriate organizations.

Accomplishments: As of March 1981, an extensive baseline questionnaire has been developed and administered to some 500 students at the Center for Labor Studies in New York City. The purpose of the questionnaire is threefold: (1) to determine the baseline levels of knowledge related to occupational cancer; (2) to determine the baseline level of exposure to a variety of carcinogens and student-worker experience working with hazardous substances; and (3) to maximize student input into the design of the curriculum through identifying and ranking learning priorities. In addition, a number of in-depth interviews with students have been conducted to help identify interests and concerns. The results of the baseline survey will guide the design of the curriculum. The curriculum will be a collaborative effort, with input from the faculty at Johns Hopkins as well as SUNY Centers in Albany and New York City.

Two advisory groups have been organized; one representing students, trade workers, trade union members and community groups and the other health and education professionals. The advisory groups have been established independently at both the Albany and New York City campuses.

Plans: The occupational cancer curriculum is expected to be developed and ready for pretesting during the 1981 summer session. After revisions the curriculum will be fully presented during the 1981 fall semester in two modes: classroom instruction in New York City, and individualized teaching in Albany. After evaluation of the curriculum, a final revision of the curriculum and independent study guidebook will be available for dissemination to other institutions and interested organizations. Finally, the model program will be presented in a regional conference at Empire State College in Albany and a national conference at Johns Hopkins School of Hygiene and Public Health in Baltimore, Maryland.

Program Director: Andrew F. Hegyeli, D.V.M., Ph.D.

Grant 27582: Community-Based Intervention for High-Risk Workers

From 08/15/80 to 08/14/82

FY 81: \$304,213 (Estimated)

Dr. Knut Ringen, Workers' Institute for Safety and Health, 1126 16th St., N.W., Washington, D.C. 20036

Objectives: To develop a model program of community-based cancer prevention and intervention for cohorts of workers and their families who have been identified as being at a high risk of cancer due to past workplace exposure to hazardous agents. The aim is to institutionalize this program in the labor movement and to replicate successful results widely throughout the labor movement. The program incorporates the following elements: (1) identification of cohorts of workers (and their families) who are at unusually high risk due to past exposure to carcinogens in the workplace; (2) determination of the needs of the cohorts, and identification of available community resources to provide medical surveillance, early detection and treatment where possible, and care to the terminally ill, as well as identification of sources of financial, legal and emotional support; (3) individual, family and peer group education in the referral and use of identified resources to promote financial, legal and emotional security through the mobilization of available resources.

Accomplishments: Substantial accomplishments have been made in the first six months of this grant. An eleven-point general model of intervention has been developed, which is being applied with flexibility to three populations:

1. The Augusta, Georgia, High Risk Project, where 1152 currently living nonunion workers face an estimated 20-90 fold relative risk increase for bladder cancer due to potential past workplace exposure to beta-naphthylamine. This project is conducted jointly with the National Institute for Occupational Safety and Health.

Specific Accomplishments: (1) A community steering committee has been established with membership from labor unions, community groups, industries and public health; (2) numerous information sessions have been held for concerned community and medical groups; (3) medical protocols have been developed, including extensive research for validation of different urine cytology systems; (4) detailed questionnaires, medical forms, reporting systems and data analysis methods have been designed; (5) planning of ongoing uniform medical surveillance and reporting systems has begun.

2. The Pattern Makers' League of North America, with 12,000 current and about 3,000 former members who have a doubled risk of cancer of the colon and rectum. This membership is located in 36 states and is employed in about 1,000 workplaces. The project is being conducted with medical advice from the Yale University General Occupational Medical Program.

Program Director: Andrew F. Hegyeli, D.V.M., Ph.D.

Specific Accomplishments: (1) Six educational workshops have been held in different regions of the country; (2) an educational booklet has been prepared for mailing to the homes of every member; (3) a uniform medical protocol and reporting system has been designed; (4) subcontracts have been negotiated for ongoing uniform medical screening for 6,000 workers in many localities involving approximately 60 employers; (5) the identification of local medical providers willing to participate has been completed.

3. The Port Allegany Asbestos Health Program, where approximately 1,100 members of the Flintglass Makers' Union have a high risk of cancers associated with workplace exposure to asbestos. This project is conducted in collaboration with the Mount Sinai School of Medicine's Environmental Sciences Laboratory, which in 1979 conducted a screening of about 350 members of the cohort.

Specific Accomplishments: (1) Established community steering committee consisting of union, management, community groups and medical providers; (2) community meetings to inform affected workers have been held; (3) planning for a second round of screenings has been completed; (4) an ongoing medical surveillance program, including medical protocols and reporting systems has been designed; (5) assistance has been provided in the development of ongoing financial support for program.

Plans: Efforts will be made to complete a medical examination of all members of the three cohorts identified above and to complete initial data analysis by the end of 1981. Additionally, we expect to have institutionalized self-sustaining and ongoing intervention programs for these cohorts.

Replication of successful results will begin for a large number of workers in different occupations with high bladder cancer risks, relying on the concerned unions to implement the program nationwide.

To further develop the model program, plans call for the identification of additional cohorts with different cancer risks, and will include at least one construction trade.

Grant 27630: Identification and Evaluation of Counseling Techniques for Cancer Patients

From 05/01/80 to 04/30/81 FY 81: \$15,852
Pamela G. Watson, Boston University, 635 Commonwealth Avenue,
Boston Massachusetts 02215

Objectives: This study proposes to explore the effects of short term supportive personal adjustment counseling during the post operative period on problems of low self-esteem and negative self worth in patients undergoing cancer/ostomy surgery. The study is for a period of one year, five months. The study population consists of patients diagnosed as having colorectal or bladder cancer for whom colostomy or urostomy surgery is the recommended treatment.

Plans: The study plans to recruit 30 subjects in a six-month period to test the hypothesis that individuals undergoing cancer urostomy or colostomy surgery who receive short-term counseling while hospitalized during the post operative period will demonstrate a significant positive alteration in the self concept, and subsequent adjustment as compared with those who do not receive such counseling.

Accomplishments: The project was approved for funding as of April 1, 1980. The project period has been extended to September 30, 1981. Data collection began in February 1981. The number of hospitals, from which subjects are being recruited for the study, has been increased from three to five. There are no further accomplishments to be reported at this time.

Program Director: Lawrence D. Burke

Grant 27638: Predictive Psychologic Study of Breast Reconstruction

From 05/01/80 to 10/31/82 FY 81: \$73,662
Dr. Jimmie C. B. Holland, Memorial Hospital for Cancer and
Allied Diseases, 1275 York Avenue, New York, New York 10021

Objectives: The objective of this study is to identify reasons why some women, and not others, ask for breast reconstruction following mastectomy and to predict from the preoperative and surgical status, which women can be expected to have acceptable surgical results and which women on psychologic grounds will likely be satisfied with a reasonable surgical result.

Accomplishments: The investigative procedures and methods of data collection have been finalized; this includes completion of all pre- and post-operative (surgical, psychiatric and self-report psychological) rating forms.

More than half the total sample number of 150 have been entered onto the study. Many of those women have had surgery within the last couple of months, and will soon be contacted for the post-operative assessments.

Arrangements were made with the Chief of the Breast Service at Memorial for access to the comparison (mastectomy patients who do not seek reconstruction) group. He has been very cooperative, and that data collection is also proceeding smoothly.

Plans: The study will compare 150 women who come to the Breast Reconstruction Clinic for evaluation with 50 women matched for age and time since mastectomy, who have chosen to wear a prosthesis. They will be evaluated on both surgical and psychologic parameters.

Program Director: Rosemary Yancik, Ph.D.

Grant 27676: Assessing the Effects of Counseling Cancer Patients

From 07/01/80 to 06/30/83

FY 81: \$228,532

Laura B. Gordon, Ph.D., Principal Investigator, Rush-Presbyterian-St. Lukes Medical Center, Chicago, Illinois 60612

Objectives: Patients with a new diagnosis of cancer of the breast, colon/rectum, bladder/prostate, and Hodgkin's disease/lymphoma will participate in a randomized study to determine the effectiveness of selected counseling techniques--individual supportive group, and educational group--in helping them cope with their illness. There is also a non-intervention control group. While counseling has generally been accepted as important in facilitating adjustment to the diagnosis of cancer, the most helpful counseling modality has not been identified in a systematic fashion. The general research questions are: (1) what personality and psychosocial variables are predictors of who will benefit from counseling and from what types of counseling; (2) what changes, if any, in patients' sense of vulnerability and in their ability to cope occur as a function of counseling; and, (3) what are the best points in time for counseling intervention?

Accomplishments: During the period October 1, 1980, to September 30, 1981, we expect to enroll approximately 50 patients in the study. (Based on a projection from current data (11/01/80-04/15/81), about one-third of these patients will randomize into individual counseling, one-half will participate in the support and educational groups and one-sixth will be part of the non-intervention control group.) People who have entered the study so far tend to be breast or Hodgkins' patients, although all other cancer sites have been represented. All counseling interventions are underway. Frequently, more than one section of the support and educational groups run simultaneously. Much of the work during the current period involved meeting individually with attending physicians to describe the study in detail and to enlist their cooperation in the referral process. Their outstanding support has contributed significantly to the success of the investigation; up to this point patient recruitment has been somewhat slower than anticipated. However, this is more a function of the lack of available patients who need the criteria for entry into the study than to either physician or patient resistance.

At the time, of writing this summary, data analysis has not yet been initiated. While psychosocial and personality data are being collected upon entry into the study, upon completion of eight weeks of counseling, and at 6, 12, and 18 months post-intervention, no subject has yet reached the 18 month point. Patients who have had counseling report that they have been able to make a better adjustment. Careful review of their counseling sessions reveals that patients have experienced a subjective sense of improvement in the areas of vulnerability, symptom distress, and interpersonal interaction (family and friends) which has facilitated their ability to cope. Conclusions as to the relative effectiveness of the counseling interventions are premature. Anecdotally, it is our understanding that patients participating in each of the interventions have

Program Director: Sandra M. Levy, Ph.D.

found them useful in their attempts to adjust to their diagnoses and the altered life styles and psychologies that they imply.

Plans: Patient recruitment will continue actively with a goal of obtaining 200 subjects by the end of the project period. Contact with nursing staff and staff physicians will be renewed to ensure the availability of patients appropriate for the study. Data collected at entry into the project, immediately following intervention, and at 6, 12, and 18 months following intervention will provide information regarding the suitability of specific counseling modalities for people with cancer and the types of coping styles developed by patients as a result of counseling.

Grant 27683: Improved Cancer Care Thru A Home Program

From 09/01/80 to 08/31/82 FY 81: \$112,779
Dr. Vincent Vinciguerra, Division of Oncology, North Shore University Hospital,
300 Community Drive, Manhasset, New York 11030

Objectives: This study is designed to test the hypothesis that home-based medical, nutritional and social support provided by a mobile van service of a university hospital's Oncologic division can modify the terminal stages of the cancer patient's disease.

Patients with histologically documented, metastatic neoplasia, who exhibit a Karnofsky index less than 50, with a life expectancy of 2 to 24 weeks are offered the home-van program on the basis of residency within 10 miles of the hospital. A comparable group of patients selected on the basis of residence outside the mobile-van catchment area receive hospital-based care.

This intervention is assessed by differences in survival time, analgesic use, cachexia, psychosocial assessment and cost/benefit between the two groups.

Accomplishments: Data abstracting forms have been designed to provide a structured framework for collecting demographic, nutritional, psychosocial, medical and financial data for the patients accessioned to the study.

Through the first six months, 75 patients have been accessioned to the study with 58 patients receiving home-based care and 17 patients receiving continuous care in the hospital. The median ages of patients who have received home-based care and inpatient care are 63 years (range: 37-85 years) and 62 (range: 34-77 years), respectively. The female/male ratios for the hospital-care group and home-care group are 3.25 and 1.23 respectively. The distribution of cancer grouped by organ system for patients receiving home-based care vs. hospital based care is: lung - 20.7% vs. 0%, GI - 27.6% vs. 11.8%, breast - 13.8% vs. 23.5%, male and female reproductive organs - 10.3% vs. 17.6%, leukemias and lymphomas - 12.1% vs. 29.4%, and for other sites - 15.5% and 17.6%, respectively.

Support of the group of patients receiving home-based care has required 278 visits by the HOME van team comprised of a medical oncologist, nurse oncologist, medical technologist, social worker and nutritionist. During the first months of the program, the physician accompanied the team on 36% of all visits.

Thirty-nine patients who have been accessioned to the study have expired. The average number of days from accession to death for the 29 patients who received home-based care was 38.3 as compared to 23 days for 10 patients who received continuous care in the hospital. Sixteen of the twenty-nine patients who were accessioned to the HOME van intervention died at home. These twenty-nine patients spent 19% of the total 1,111 days on study in the hospital.

Plans: Our major objectives for the coming year are to continue accessioning patients to the study for a total of more than 180 patients and to complete the data acquisition phase of the project. A computerized data base containing all clinical and economic variables will be developed to permit assessment of the

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reliability of the data and to allow statistical analysis. This study should provide critical information on an alternative method of supportive care for future health programs for terminal cancer patients and their families.

Publications:

Vinciguerra, V., Degnan, T., Diener, J., Budman, D., Schulman, P., McCartney, J., O'Connell, M. and Vargas, M.: Home Oncology Medical Extension (H.O.M.E.): A new home treatment program. CA 30:182-185, 1980.

From 08/01/80 to 06/30/83

FY 81: \$52,829

Dr. Ronald Gier, University of Missouri-Kansas City School
of Dentistry, 650 E. 20th St., Kansas City, Missouri 64108

Objectives: This program is designed for undergraduate dental students to:

(a) provide instruction in the biologic, biomedical, pathological and psycho-social aspects of cancer; (b) train students how to examine for, detect and definitively diagnose malignant diseases of the head-and-neck; (c) train students to evaluate and treat the oral conditions of patients who are about to undergo, and who are undergoing, radiation of the head-and-neck, or chemotherapy; (d) participate in tumor boards or tumor registries. The program will also provide continuing education for interested health professionals.

Accomplishments:

1. Development and presentation of an Oncology Course for undergraduate dental students. Presenters include guest lecturers and faculty of the dental schools.
2. Development of two continuing education programs.
3. Planning for student rotation through the Head-and-Neck Clinic and student follow-up of assigned head-and-neck cancer patients. Implementation to begin in the spring of 1981.
4. Organization of closed circuit television and case study conference room for students to study on-going and completed cases.

Plans:

1. Develop supplementary materials for the Oncology Course
2. Evaluate student performance in all phases of the program
3. Present two continuing education programs
4. Increase the patient pool of the Head-and-Neck Clinic by arranging a cooperative referral agreement with hospitals in the counties immediately surrounding Kansas City.
5. Determine the feasibility of including dental hygiene students in the program
6. Employ a clinic coordinator who will supervise students in the Head-and-Neck Clinic.
7. Develop case materials of patients being treated
8. Design a computer simulation of head-and-neck cancer detection and diagnosis.

Program Director: Margaret H. Edwards, M.D.

Grant 27767: Counseling Techniques for Cancer Patients

From 04/01/80 to 03/31/82

FY 81: \$96,222

Dr. Ernest I. Kohorn, Yale University, New Haven Hospital, 789 Howard Avenue,
New Haven, Connecticut 06504

Objectives: This project will study modes of counseling for female patients with cancer of the reproductive organs. A group counseling format in which patients receive information and support through each other in a structured group setting will be compared with other forms of counseling. Ninety patients will participate in one of three counseling procedures: thematic group counseling, individual group counseling and standard counseling. The third group will actually serve as an attention-placebo control group.

Accomplishments: Since the study began, 60 women have met the eligibility criteria for the study, and 51 have agreed to participate. This response certainly reinforces our expectation of the need for counseling in this population. The 51 women range in age from 35 to 75 years, with a mean age of 58 years. They are mainly white and of middle income. All the expected sites of gynecological cancer are represented. Forty-eight percent of the women were diagnosed with endometrial cancer; 23 percent cervical cancer; 23 percent ovarian cancer; 5 percent vulva cancer and 3 percent vaginal cancer.

Pre-counseling Assessments - Data reported here was elicited during a structured interview conducted within one month of diagnosis following the formats of the Psychosocial Adjustment to Illness Scale and the Hamilton Depression and Anxiety Scales.

The preliminary data supports the conclusion that responses of these women would exhibit depression and anxiety. Seventy-one percent reported mild to moderate depression. Fifty-four percent reported mild to moderate symptoms of anxiety by such responses as "feels tense," "loss of interest in activities," "poor memory," "worried."

Difficulties and impairments in five areas of social adjustment were examined: vocational, domestic, sexual, leisure and social.

Of the 16 women who were employed at the time of diagnosis, 12 (75%) reported mild to marked vocational impairment with 52% being out of work for 2 weeks or longer. Although cancer diagnosis and treatment substantially impaired domestic function of 40% of the women, 76% reported that their family members adapted by shifting roles to perform household duties and tasks.

Fifty-three percent of the women reported a slight to significant decrease in participation in leisure activities. Forty-two percent reported a decrease in social activities.

Significant impairments were found in sexual adjustment. Of the 23 women who were sexually active prior to diagnosis, all reported disruption of sexual activity following the diagnosis of cancer.

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Counseling - of the 51 women participating in the study 45 have been randomly assigned to one of three counseling procedures. Sixteen women were assigned to group counseling, 13 to individual counseling and 16 to standard counseling. At this time 33 women have completed counseling. Conclusions regarding differential influence of counseling await the accumulation of a sample of appropriate size. This will be accomplished within the first 3 months of the second year of this project.

Except for the need to reach the desired sample size, the research has progressed without technical problems.

Plans:

- (1) To study as early as possible in the second year an additional number of patients to acquire the desired sample size of 90 women.
- (2) To continue to conduct thematic individual and thematic group counseling.
- (3) To compare the effect of the group and individual thematic counseling procedures on psychosocial adjustment shortly after counseling.
- (4) To look specifically for changes in anxiety level, depressive reactions and social adjustment of patients within each counseling mode.
- (5) To re-evaluate the effects of those counseling procedures at a point in time 9 months from diagnosis.

Grant 27807: Social Support and Adaptation in Terminal Lung Cancer

From 05/01/80 to 04/30/83

FY 81: \$121,638

Dr. Richard J. Goldberg, Associate Director, Department of Psychiatry, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02902

Objectives: In this study we propose to evaluate the effects of social support on the psychosocial adaptation of terminal lung cancer patients. We have carefully defined both social support, our independent variable, and psychosocial adaptation, our dependent variable. We will look at both the patient and the patient's significant supporting figure from bio-psycho-social perspectives including: psychological factors which may influence receptivity to support, as well as how a person experiences and deals with a major stress; biologic factors which may account for a significant portion of the patient's distress; and social system factors. A clearly specified counseling intervention will be provided for one group of patients' support figures.

Accomplishments: An interdisciplinary team composed of a psychiatrist as principal investigator, two psychologists, and a masters level social worker organized and implemented the research protocol which began to accrue patients in the fall of 1980. By forming working liaisons with a number of oncology clinicians, approximately 3 lung cancer patients enter the study each week. The draft of a Support Counseling Manual was completed and has formed the basis for a specified intervention. By September 30, 1981 we anticipate data collection on approximately 90 patients and their supporting figures.

Plans: The major continued research activity will be continued follow-up of subjects with questionnaires and the counseling intervention. Initial data evaluation will take place in September 1981. We are considering measurement of ectopic hormone production in our lung cancer patients and will coordinate that information with other psychosocial data. Following the deaths of lung cancer patients in the study, we intend to look at the physical morbidity and psychosocial adjustment of the patient's significant supporting figure over a one to two-year period.

Program Director: Lawrence D. Burke

From 05/01/80 to 04/30/83

FY 81: \$194,864

Dr. James Prochaska, University of Rhode Island, Kingston, Rhode Island 02881

Objectives: Smoking cessation research among self-quitters to date has generated a revolving door model of change that has discriminated processes of change used by self-quitters from those used by subjects in formalized treatments. Self-quitters revolve through a cyclical series of stages an average of three times prior to permanently exiting from their habit of smoking. Different change processes are used to progress through each of the stages. Subjects differing on age, sex and SES use some particular processes more than others. The objective of the proposed research is to advance our present understanding of the processes used by self-quitters to enter the revolving door of change, to progress through each stage and to exit into a non-smoking life style.

Accomplishments: One-thousand subjects were recruited representing five key stages of change: precontemplation, contemplation, action, maintenance and relapse. These subjects completed an extensive retrospective and current questionnaire, an interview and a saliva test for smoking status. Preliminary analyses of the change processes section of the questionnaire are extremely encouraging, since the factor structure of this instrument is very consistent with the revolving door model of change. Specifically, we have a 40 item test that yields 10 highly reliable and strongly defined scales for measuring 10 distinct processes of change. The processes are: (1) Consciousness Raising; (2) Self-Reevaluation; (3) Environmental Reevaluation; (4) Self Liberation; (5) Social Liberation; (6) Counterconditioning; (7) Stimulus Control; (8) Contingent Reinforcement; (9) Dramatic Relief; and (10) Helping Relationship. Furthermore, the data demonstrate that as predicted from our model, there are highly significant relationships between the stage of change subjects are in and the processes of change that they use most. Specifically, immotive members in the precontemplation stage use denial and active avoidance to resist any internal pressure to change. Contemplaters emphasize consciousness raising and self-reevaluation, with self-reevaluation procedures appearing to be the process that allows for the transition from contemplater into action. Recent quitters in the action stage use the most processes with self-reevaluation, self-liberation, contingent reinforcement, counterconditioning and stimulus control being emphasized in social liberation deemphasized. The maintenance group appears to emphasize counterconditioning and stimulus control procedures, though they also have the benefit of having succeeded in earlier stages of change as well. The relapsers appear to revolve right back into contemplation.

Program Director: Catherine S. Bell, M.S.

Plans: The 1,000 subjects are currently completing the first six-month follow-up of a two-year prospective study. This study will allow us to process the importance of each change process in facilitating movement through each stage of change into either long term smoking cessation or relapse. Other behavioral cognitive and system changes will also be related to the longitudinal changes the subjects make in their smoking status. A comparative outcome experiment will test the hypotheses that self-quitters can be as successful as subjects in traditional formalized treatments and that these treatments can be improved through the application of data from self-quitters. A controlled experiment will test the hypothesis that the dissemination of information from the longitudinal work can improve the success rate of smokers who quit on their own.

Grant 27912: Evaluation of Counseling for Mastectomy Patients

From 05/01/80 to 04/30/83

FY 81: \$126,316

Dr. Gary Bond, Northwestern University, Institute of Psychiatry,
Evanston, Illinois 60201

Objectives: This project proposes to evaluate the effectiveness of short-term counseling approaches in helping mastectomy patients cope with the psychological problems resulting from the diagnosis and treatment of cancer. A comparative experimental design evaluating the effectiveness of four different counseling approaches, each addressing a specific coping task facing the mastectomy patient, will be carried out in ten counseling sessions over a ten-week period following surgery. The proposed approaches include individual psychodynamically-oriented counseling, a peer-oriented support group, informational lectures, and group teaching or relaxation techniques and stress management.

Accomplishments: Between May and September 1980 we interviewed over 50 prospective candidates in the Chicago area to serve as counselors for our program. From these, we selected eight female psychotherapists each with more than five years experience in her respective modality (five Ph.D. psychologists, one M.S.W., and two Masters-level nurses). They attended an orientation seminar on the medical aspects of mastectomy and worked with senior consultants in developing detailed curricula conforming to the research protocol. Also during this time we developed a three-hour research interview to be administered prior to, immediately following, and six months post counseling. This interview combined both standardized and tailor-made instruments spanning a wide range of issues of relevance to cancer patients, and piloted for its sensitivity and relevance to mastectomy patients. We developed a tracking system for identifying potential subjects undergoing surgery at Northwestern Memorial Hospital. It consists of a review of daily operation schedules, confirmation with and permission from the patient's surgeon, a brief in-hospital visit with the patient describing the study and giving her a brochure explaining our project, and a follow-up phone call three weeks later. In November we began recruiting subjects by sending follow-up letters to women whose surgeries occurred during the preceding three months. In January the first cohort began counseling. All counseling sessions are tape-recorded and will be subject to a content analysis. As of this writing, 63 potential subjects have been contacted; 17 have been interviewed, and 12 have begun counseling.

Plans: Negotiations are now underway to extend our recruitment to other hospitals within the Chicago area to speed the rate of forming counseling groups. We intend to complete our target sample of 96 subjects by May 1982.

Program Director: Lawrence D. Burke

From: 09/01/80 to 05/31/83

FY 81: \$64,340

Dr. Robert B. Hurlbert, The University of Texas System Cancer Center, M.D.
Anderson Hospital & Tumor Institute, 6723 Bertner Avenue, Houston TX 77030

Objectives: Our objective is to explain the difference in pyrimidine metabolism between susceptible and resistant tumors and tissues. This should help in the recognition of susceptible tumor types and in choosing effective drugs or combinations. The experimental objectives are to define in vivo the critical parameters in biosynthesis of the pyrimidine nucleotides in terms of the balance between the de novo and salvage pathways. Drug-responsive colon tumors in mice and rats will be compared with normal tissues and resistant tumors, and the interaction of host, tumor and drug via blood-borne pyrimidine nucleotide precursors will be studied. The action of rationally-devised combinations of drugs on synthesis of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) in target tumors will then be explored. Appropriate analyses for the determinant parameters of selective action of pyrimidine antimetabolites will be devised with the goal of providing applicability in clinical studies.

Accomplishments: Since high pressure (performance) liquid chromatography (HPLC) does not resolve uracil, uridine and cytidine from other tissue components well enough to provide sensitive quantitation, we have worked out an enzymic - P^{32} -labeling method capable of estimating endogenous levels of these pyrimidines in blood and tissues. At 24 and 48 hours after injection of 6-C¹⁴-orotic acid, the liver uridine nucleotides remain highly labeled with continuing conversion to RNA. Labeled uridine and uracil are present in the liver, each about 2% of the nucleotide label. Most of the label is in the blood cells as uridine nucleotides, but the plasma contains labeled uracil, uridine and a trace of cytidine. Uracil contains more label than uridine. The interpretation is that the blood does contain significant amounts of uracil and uridine, possibly in equilibrium with liver pyrimidines, and these are available as precursors for any tissue or tumor capable of utilizing them.

When labeled 2-C¹⁴ uracil is injected, it is rapidly cleared from the blood, much of it being excreted in the urine. It is poorly retained as such by the liver and poorly incorporated into the liver nucleotides. It is, however, concentrated as such by the tumor and incorporated into nucleotides better than in the liver. Little uracil is converted into uridine. Injected labeled 5-H³-uridine is also degraded and excreted, although not as quickly as uracil, and is fairly well retained by liver and incorporated into liver nucleotides. In the tumor, more of the label is present as uracil than as uridine, and incorporation into tumor nucleotides is much less than into liver nucleotides. Administration of N-(phosphonacetyl)-L-aspartate (PALA) (5 mg/kg, 24 hours) causes an increase of incorporation of both uracil and uridine into both liver and tumor.

Plans: We propose to explore ways to evaluate the relative dependence on de novo and salvage pathways, normally and during treatment with pyrimidine antimetabolites. Since only traces of label are incorporated into tumor pyrimidine nucleotides in vivo, we will experiment with various ways of slicing or mincing tumor tissues to obtain relevant systems capable of comparing de novo and salvage pathways.

Program Director: Vincent J. Cairoli, Ph.D.

From 05/01/80 to 04/30/83

FY 81: \$59,481

Dr. Robert L. Baehner, Indiana University, 1100 West Michigan Street,
Indianapolis, Indiana 46223

Objectives: The objectives of this study are to evaluate the effectiveness of enteral and parenteral nutrition in preventing and/or reversing protein energy malnutrition (PEM), maintaining or restoring immune competence, preventing treatment delays, and improving tumor response of 36 children with stages III/IV neuroblastoma who are receiving chemotherapy (5 drugs: cytoxan, vincristine, DTIC, adriamycin, VM-26) every three weeks. In addition, anthropometric and biochemical indicators of clinical and subclinical PEM in children with neuroblastoma will be identified.

Accomplishments:

- A. Patient accrual has continued at approximately 10 per year. Considering patients entered prior to approval of the grant, 19 patients are entered onto the study of which 17 have evaluable serial data. One died at one week post diagnosis and the other had prior treatment so was ineligible for analysis. The following summarizes the clinical characteristics of this group:

Age: median 26.5 month (range 6 months to 10 years)

Sex: 9 female, 10 male

Stage of Disease: 1 State III, 18 Stage IV

Oncologic Treatment Protocol: Children's Cancer Study Group No. 371

As defined by the randomization in the nutrition study protocol, patients were randomized to appropriate nutrition treatment within their nutritional status classification.

Nutritional Status
At Diagnosis

Nutrition Treatment

6 Nourished

6 Enteral Nutrition (non-randomized prior to grant approval)

2 Nourished

1 Enteral Nutrition
1 Total Parenteral Nutrition

9 Malnourished

4 Partial Parenteral Nutrition with Enteral Nutrition
5 Total Parenteral Nutrition
17 Total patients

- B. The implications of nutritional staging at diagnosis as a predictor of duration of remission and survival at one year of treatment was evaluated in 19 of the children. Children were classified as either nourished or malnourished, based upon the following criteria: weight for height 5th percentile, weight loss 5%, or serum albumin 3.2g/dl. Ten children were

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considered nourished; nine were considered malnourished at diagnosis. Based upon life table analyses, the length of remission and survival at one year of children classified as nourished at diagnosis were significantly improved.

Plans:

- A. We plan to continue to accrue patients onto the study. We anticipate registering another 10 patients during the 02 year of this grant.
- B. Our first group of patients will have progressed beyond 22 weeks of treatment (the end of the study period). We plan to begin preliminary evaluations of this group.
- C. We will complete a preliminary evaluation of short term changes in nutritional status related to low energy intake during 5 day cycles of chemotherapy. Subtle, short term, objective changes may herald treatment modifications which would adversely affect tumor response.
- D. Preliminary data which formed the basis for this grant proposal has been presented at the Western Hemisphere Nutrition Congress, August 12, 1980 (Los Angeles, California) and the National Cancer Institute sponsored Pediatric Cancer and Nutrition Workshop, December 11-12, 1980. These presentations will be published in the Annals of the New York Academy of Sciences and in Cancer Research (see publications).

Publications:

Rickard, K.A., Baehner, R. L., Provisor, A. J., Weetman, R.M., and Grosfeld, J. L.: The Effects of Hyperalimentation on Immune Function and Tumor Growth. Ann. N.Y. Acad. Sci., (IN PRESS)

Rickard, K.A., Baehner, R. L., Coates, T. D., Weetman, R. M., Provisor, A. J., and Grosfeld, J. L.: Pediatric Cancer and Nutrition: Supportive Nutritional Intervention. Cancer Res. (IN PRESS)

From 09/01/80 to 05/31/83

FY 81: est. \$115,284

Dr. T.V. Zenser, Geriatric Center, VA Medical Center, St. Louis, Missouri;
and St. Vincent Hospital, Worcester, Massachusetts

Objectives: The overall object of this project is to test the hypothesis that the initiation of urinary bladder cancer by certain chemicals is a result of metabolic activation by prostaglandin endoperoxide synthetase (PES). It is proposed that the prostaglandin hydroperoxidase rather than the fatty acid cyclooxygenase activity of PES is responsible for this activation. Characteristics of aerobic and anaerobic N-/4-(5-nitro-2-furyl)-2thiazolyl/ formamide (FANFT) and 2-amino-4-(5-nitro-2-furyl)-thiazole (ANFT) metabolism will be examined. The ability of aspirin, an inhibitor of prostaglandin synthesis, to prevent the induction of urinary bladder cancer in rats fed FANFT will be examined.

Accomplishments: Microsomes prepared from rabbit bladder transitional epithelium, renal inner medulla, and ram seminal vesicles metabolized FANFT and ANFT aerobically. This metabolism was dependent upon specific fatty acid substrates (arachidonic acid) and inhibitors (aspirin, indomethacin) of PES. Organic hydroperoxides such as cumene hydroperoxide and 15-hydroperoxy-5,8,11,13-eicosatetraenoic acid also initiated metabolism. The latter was not prevented by aspirin or indomethacin but was inhibited by the antioxidants vitamin E, ethoxyquin, and butylated hydroxytoluene. Hydroperoxide-mediated metabolism is ferric heme dependent. Products of FANFT and ANFT metabolism purified by HPLC showed distinct uv spectra. These metabolites have been tentatively identified as lactones. Results are consistent with aerobic metabolism of FANFT and ANFT by the hydroperoxidase activity of PES. Anaerobic metabolism of FANFT by bladder microsomes (0.3 ± 0.002 nmol/mg/min) was 64-fold less than PES (19.4 ± 1.3 nmol/mg/min). Both the enzymatic and chemically reduced FANFT metabolite was identified by mass spectra to be a nitrile. Aspirin does not inhibit FANFT nitroreduction. In rats fed a diet of 0.5 percent aspirin and/or 0.1 or 0.2 percent FANFT, aspirin inhibited the appearance of light microscopically observed hyperplastic lesions induced by 6 or 12 week FANFT feeding. Foci with ropy microridges or uniform or pleomorphic microvilli observed by scanning electron microscopy were reduced by feeding aspirin with 0.2 percent FANFT and their appearance was completely inhibited with 0.1 percent FANFT. Aspirin reduced bladder PGE₂ content. These results suggest that PES is involved in the initiation of FANFT-induced bladder cancer.

Plans: Subsequent studies will be the following: (1) identify ANFT nitroreductase product, and PES-mediated FANFT and ANFT products, (2) having identified FANFT and ANFT reduced and oxidized products, examine rat urines from FANFT feeding study for similar products, (3) complete the in vivo FANFT rat feeding study, and (4) determine the binding of PES-mediated ¹⁴C-FANFT and/or ¹⁴C-ANFT products to macromolecules.

Program Director: William E. Straile, Ph.D.

From 05/01/80 to 04/30/84

FY 81: \$265,079

Dr. Jerome J. DeCosse, Memorial Hospital/Cancer, Allied Diseases,
1275 York Avenue, New York, New York 10021

Objectives: The current study is designed to determine the effectiveness of intensive nasogastric feeding compared with optimal oral nutrition in patients with advanced head and neck cancer who are treated with radiation therapy. The overall goal is to evaluate the effects of aggressive nutritional support on the patient's ability to tolerate and respond to radiation therapy and, in some cases, chemotherapy, as well as its effects on tumor recurrence and patient survival.

Questions to be studied include the relationship of nutritional status to therapeutic response, the differences between groups in caloric and protein intake, body weight, amount and duration of therapy and severity of illness. The most effective techniques for improving patient nutrition, both orally and extra-orally; and the long-term consequences of aggressive nutritional support during short-term therapy.

Findings from this study should provide data on the efficacy of nutritional support during radiation therapy to the head and neck and on the most effective means of delivering adequate nutrition to out-patients with head and neck cancer.

Accomplishments: Since September 1980, study personnel have been appointed and trained in methods of providing aggressive nutritional support to patients with advanced head and neck cancer; the data base has been designed, implemented and tested and the study procedures have been integrated into ongoing hospital routines.

Eleven patients have been entered into the randomized trial; seven patients are in the oral nutrition group and four patients are in the tube-fed group. Additionally, a group of ten patients have been followed during their therapy and given intensive oral nutrition counseling. These patients were eligible for the study, but for various reasons were not entered (e.g. patients who were leaving the geographic area before prescribed follow-up procedures could be completed or patients who would not accept randomization into the tube-feeding or oral nutrition groups). These patients have provided valuable patient contact and counseling experience, and information has been rigorously collected from these patients to provide background information for our study population.

Preliminary data suggests that patients in both groups have significant body weight loss when initially seen for radiotherapy. Mean daily caloric intake before radiation treatment has varied from 650 KCal per day to approximately 1600 KCal per day. During radiation therapy, oral intake ranged from 800-2000 KCal in the oral group, and 500-2500 KCal in the tube-fed group. This dietary intake was reflected in a mild degree of weight loss (1 to 4 kg) in both the oral and tube fed groups. Thus, both groups had insufficient caloric and protein intake to maintain optimal nutrition during their radiation therapy. To encourage better compliance by patients, we have involved family members, provided nutritional

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supplies, and nutritional supplements and contacted patients frequently at home and in the clinic in person. Techniques for further improvement of patient compliance is an important ongoing activity of the study.

Data collection forms have been standardized and on-line computerized data entry is recorded on all study patients and the eligible non-study group. In addition, considerable effort has been made to integrate the activities of this multi-disciplinary study into the routines of the out-patient department. This goal has been fulfilled through efficient systems for identifying and following patients in the Head and Neck, Radiation Therapy, and Chemotherapy Clinics as well as hospitalized patients.

During the five-month study period, considerable practical experience has been achieved applying nutritional methods to head and neck cancer patients undergoing radiation therapy. Techniques in oral and tube feeding nutrition support, methods to improve patient compliance and nutritional monitoring techniques are being developed which should prove to be valuable to others working with head and neck cancer patients as well as with other malignant diseases.

Plans: Patients' accrual will continue to compare the effects of naso-gastric tube feeding with optimal oral nutrition in patients with advanced head and neck cancer. Major goals will be to identify those mechanisms by which optimal oral and naso-gastric nutrition can be most effectively achieved with consistent follow-up care. The rates and duration of response to radiation therapy and chemotherapy, patient survival and quality of life in these two groups of patients will be evaluated.

From 12/01/79 to 11/30/82

FY 81: \$62,687

Dr. Bernard Kliman, Endocrine Unit, Massachusetts General Hospital, Fruit Street, Boston, Massachusetts 02114

Objectives: Prostatic diseases involving benign hyperplasia or cancer are thought to be influenced by androgen stimulation. This project is intended to evaluate the role of circulating testosterone and tissue receptors for androgen in the control of prostate cell metabolism and growth. We have developed a human model system based on suppression of testosterone levels in men awaiting open surgery for benign prostatic hyperplasia. Synthetic agents are administered in the form of estrogen, diethylstilbestrol, or progestational anti-androgen, megestrol acetate, or androgen, fluoxymesterone. Changes in total and unbound plasma testosterone, gonadotropins, and the cytosol and nuclear androgen receptors of excised prostatic tissues are measured in control and treated subjects, with comparisons to metastatic prostatic carcinoma. The goal is to achieve a better understanding of the mechanism of action of androgens in human prostatic cells and to formulate rational approaches to therapy of prostatic diseases.

Accomplishments: During the current year, we have characterized the specificity of a new sepharose-linked antibody reagent for quantitation of androgen receptors in cytosol and nuclear preparations. Equilibration studies confirmed the adequacy of exchange of tritium labeled dihydrotestosterone with androgen receptor sites. Fractionation experiments revealed that unchanged testosterone is likewise capable of translocation to the nuclear compartment, but that dihydrotestosterone is preferentially bound to nuclear receptor sites. Specificity studies demonstrated that the agents used to suppress circulating testosterone levels (diethylstilbestrol, megestrol acetate, and fluoxymesterone) do not interact with the androgen receptor sites. A group of 10 patients with benign prostatic hyperplasia has completed the estrogen pretreatment protocol. Their biochemical studies revealed a marked depletion of circulating testosterone after a five day course of 5 mg of diethylstilbestrol by mouth every 8 hours. This effect was associated with a diminution in the concentration of nuclear androgen receptors and a concomitant increase in cytosol androgen receptors, compatible with a recycling phenomenon.

Plan: We are continuing new studies with synthetic progestational anti-androgen and androgen. Their effects will be compared to those observed in estrogen treated patients with benign prostatic hyperplasia and in metastatic deposits of prostatic cancer. We plan to develop a systematic method for analysis of androgen receptors and to design therapeutic strategies for patients with benign prostatic hyperplasia or cancer.

Publications:

Kliman, B., MacLaughlin, R.A., and Prout, G.R., Jr.: Measurement of Androgen Receptor in Cytosol of Human Prostatic Tissues with a Sepharose-Linked Antibody System. Prostate Cancer and Hormone Receptors. Murphy, G.P., Ed. Alan R. Liss, New York, pp. 85-96, 1979.

Program Director: Andrew Chiarodo, Ph.D.

Kliman, B., Prout, G.R., Jr. and Mac Laughlin, R.A.: Characterization of Androgen Receptor in Human Prostatic Tissues and Demonstration of Decreased Androgen Receptor Content in Metastatic Prostate Cancer. Surg. Forum 30: 550-551, 1979.

Abstracts:

Kliman, B., MacLaughlin, R.A. and Prout, G.R., Jr.: Assessment of Androgen Binding to Human Serum Proteins and to Prostatic Cytosol and Nuclear Binding Sites. Lig. Quart. 3: 50, 1980.

Kliman, B., MacLaughlin, R.A. and Prout, G.R., Jr.: Effect of Diethylstilbestrol on Androgen Receptors in Human Benign Prostatic Hyperplasia. Endocrine Soc. Program of 62nd Annual Meeting, p. 282, Washington, D. C., 1980.

MacLaughlin, R.A., Kliman, B., Eddleston, M.T. and Prout, G.R., Jr.: Nuclear Translocation of Unchanged Testosterone in Cells of Human Benign Prostatic Hyperplasia. Clin. Res. 29: 507-A, 1981.

Kliman, B., Prout, G.R., Jr., MacLaughlin, R.A. and Eddleston, M.T.: Program of the Annual Meeting of the American Urological Association, Boston, Massachusetts 1981.

Kliman, B., Prout, G.R. Jr., MacLaughlin, R.A. and Eddleston, M.T.: Specificity of Androgen Receptors in Cytosol of Human Benign Prostatic Hyperplasia. Endocrine Soc. Program of the 63rd Annual Meeting, Cincinnati, Ohio. 1981.

Manuscripts in Press:

Kliman, B., MacLaughlin, R.A. and Prout, G.R., Jr.: Androgen Receptor Measurements in Cytosol of Human Benign Prostatic Hyperplasia and Metastatic Prostatic Cancer. J. Clin. Endocr.

Kliman, B., MacLaughlin, R.A. and Prout, G.R., Jr.: Specificity of a Sepharose-Linked Antibody System for Measurement of Androgen Receptors in Cytosol and Nuclear Preparations of Human Prostatic Tissues. Steroids.

Manuscripts in Preparation:

Kliman, B., MacLaughlin, R.A. and Prout, G.R., Jr.: Effects of Diethylstilbestrol on Circulating Testosterone and on Prostatic Androgen Receptors in Human Benign Prostatic Hyperplasia.

Kliman, B., MacLaughlin, R.A. and Prout, G.R., Jr.: Translocation of Testosterone to the Nuclear Compartment of Human Prostatic Cells.

From: 06/01/80 to 05/30/83 FY 81: \$60,911
Dr. Lewis M. Schiffer, M.D., Allegheny-Singer Research Corp., 320 East North
Avenue, Pittsburgh, PA 15212

Objectives: The overall goals are to evaluate human colon tumor xenografts in athymic "nude" mice as a model for human disease. In these studies cell kinetic parameters and glucocorticosteroid hormone receptor (GR) levels will be used as markers. Cell kinetic and GRs determined in primary human tumors will be compared to values later determined in serially passaged xenografts. In this way we will be able to evaluate the applicability of a xenograft model for human disease from the standpoints of cell proliferation, tumor, growth and cell function. Further, these studies may provide therapeutically useful insights regarding the hormonal regulation of colon tumor cell proliferation.

Accomplishments: Thus far, we have obtained 15 human colorectal tumors for study. Of these 15 samples, kinetic studies have been performed on 12 with 8 patients being evaluable at this time. From these 8 patients, 6 primary tumors and 2 metastatic tumors were obtained and studied. In the tumors, the thymidine labeling indices ranged from 1.5 to 17.9%, while the growth fraction estimates ranged from 21.1 - 53.6%. Tumor tissue from 8 primary colorectal tumors has been implanted into athymic "nude" mice with 2 of 8 tumors resulting in xenografts. As a result of pilot studies with a human colon tumor cell line (LoVo), we decided to evaluate GR levels in samples of human primary and/or metastatic colorectal cancer. Previous studies in our laboratory indicated that cell proliferation in normal murine colon could be inhibited with methyl-prednisolone and dexamethasone. We have accumulated data on 7 colorectal tumors. Of these, 5 were primary tumors and 2 were metastatic. All tumor samples were diagnosed as being moderately well differentiated adenocarcinomas. Two samples of "normal adjacent" colon were also studied. GRs were determined by the dextran-charcoal competitive binding assay using ^3H -dexamethasone. Six of the 7 tumors had significant levels of cytoplasmic receptor. The mean value for all tumors was 65.9 ± 13.5 fm/mg protein. All 5 of the primary tumor samples were positive while 1 of 2 metastatic samples were positive ($122.3 \pm 2.09 \times 10^{-6}$ M) were within the range seen for corticosteroid sensitive tissues. The 2 samples of "normal adjacent" colon were also receptorpositive (61.0 ± 4.5 fm/mg protein).

Plans: We will continue to accumulate both kinetic and GR data on human primary colorectal tumors and serial xenografts in nude mice. In addition to cytoplasmic GR we also plan to adapt techniques to evaluate nuclear GR in colorectal tumors. These and other studies will provide useful insight regarding hormonal regulation of colon tumor cell proliferation and the applicability of xenograft model for human disease.

Publications: None.

Program Director: Vincent J. Cairolì, Ph.D.

From 08/01/80 to 06/30/82

FY 81: 49,865

Dr. Darryl M. Williams, Louisiana State University Medical Center-
Shreveport, P.O. Box 33932, Shreveport, Louisiana 71130

Objectives: This program is designed to continue and expand a cancer teaching program for undergraduate, graduate and practicing physicians throughout the geographic area by means of (1) increased training experiences including student research activities, additional lecture series, increased numbers of electives and new conferences as well as augmented learning resources for students such as locally developed audio-visual materials and expanded self-study units; (2) coordinated longitudinal training experiences for clinical associates; and (3) expanded teaching activities in outlying hospitals and accessible educational activities within the University for practicing physicians.

The purpose of these expanded education activities is to provide a basis for the improvement of cancer care in the community.

Accomplishments: Undergraduate training has been expanded to include a weekly conference for senior medical students which is centered upon the fundamental aspects of diagnostic evaluation of the patient with neoplastic disease. There has also been included an inter-departmental conference for clinico-pathologic correlation in patients with hematologic malignancies. Elective courses in clinical pediatric hematology/oncology and bone-marrow interpretation have also been developed. Five clinical assistants have been selected for ongoing projects which include a wide range of studies including clinical surveys, evaluation of humoral substances in control of tumor growth and pathologic analysis of gastrointestinal cancer.

Audiovisual programs have been developed to augment the regular curriculum. These have included topics in hematology, breast cancer, lung cancer and cancer detection. Some of these programs have been presented to audiences throughout the northern part of Louisiana.

Visiting lectureships have also been increased. These visitors, representing the specialties of Pediatrics, Internal Medicine and Surgery have been brought from major centers to give lectures, clinics and conferences for the education of students, house officers and practicing physicians. As part of this program, a Louisiana Cancer Day has been instituted. The first visitors will be the Directors of the Surgical and Medical Oncology Programs at Louisiana State University in New Orleans. Their visit will be built around lectures and the Tumor Board.

Plans: The the coming year, the focus of the program will be to increase teaching of the psychiatric aspects of care of the patient with cancer. In addition, more effective evaluation systems will be developed to provide better assessment of the progress of the program.

Program Director: Margaret H. Edwards, M.D.

From 06/01/80 to 05/31/83

FY 81: \$166,766

Anne C. Carter, M.D., State University of New York, Downstate Medical Center, Brooklyn, New York 11203

Objectives: This project compares the effectiveness of three different educational methods in teaching and motivating women to practice breast self-examination (BSE). Women are randomly assigned to one of three teaching methods: (1) the "Cognitive" method--the conventional lecture-demonstration format; (2) the "affective" method--stresses the importance of each participant having the opportunity to hear from and share with others feelings about breast cancer, self-examination and early detection in addition to learning the accurate technique; (3) the "Mixed" method--combines elements of the "Affective" and "Cognitive" approaches. Effectiveness of teaching methods is measured by the participants' BSE skill and regularity of practice. Ultimately 900 women will be taught BSE by each of the three methods.

Accomplishments: Twenty-nine nurses were trained as of February 15, 1981. Four-hundred nine women were taught BSE: 36 percent in Cognitive sessions, 33 percent in Affective sessions, and 31 percent in Mixed sessions. In addition, 99 of these women have attended their three-month follow-up session. Demographic information for the 409 subjects indicate that the distributions of age, ethnicity and education are similar in the three groups. Overall, 15 percent of the subjects reported a family history of breast cancer, e.g., mother, sister, aunt or grandmother; of these subjects, 57 percent reported that a relative died of the disease. Just over 42 percent of the subjects had a friend or acquaintance with breast cancer.

Approximately 90 percent of the subjects reported that they had heard of BSE before the teaching session and half had been taught BSE, 27 percent by a physician or nurse and 23 percent by other means. However, only 26 percent responded that they knew how to perform BSE. One-quarter of the women reported practicing BSE monthly or more often. By contrast, 35 percent said they never practiced BSE and 20 percent said they practiced it three-six times a year. Another 20 percent said they practiced BSE once or twice a year or less.

Overall, the randomization has resulted in three comparable groups as measured by the distribution of the above characteristics as well as by others.

Recruitment of subjects at Downstate and KCH Medical Centers will be completed by July 1981. By September 1981, the three-month follow-ups will be 90 percent completed and 12-month follow-ups will begin. At this time, recruitment of subjects at the three additional sites will have begun (see below).

Plans: The project will continue at Downstate and Kings County Medical Centers while adding three additional sites in Brooklyn. Arrangements are nearing completion to provide the program to women in a large industrial

Program Director: Sandra M. Levy, Ph.D.

firm, a community college and a community health clinic. Initial teaching sessions will begin at these locations in the summer of 1981. BSE practice will be evaluated for all subjects up to one year after instruction and for subjects at Downstate and Kings County Medical Centers up to two years after instructions.

From 07/01/80 to 06/30/86

FY 81: \$56,618

Dr. Michael E. Pliskin, University of Pennsylvania School of Dentistry
Philadelphia, Pennsylvania 19104

Objective: The program is designed to train and educate undergraduate, graduate, and postgraduate dental and dental hygiene students to become competent in the detection, diagnosis and management of head-and-neck cancer with specific emphasis on oral cancer. These objectives will be accomplished by developing a program which utilizes the following educational mechanisms: Surveillance, head-and-neck cancer team and principles of referral, routine dental care for oncology patients, development of individualized treatment plans for oncology patients, home care regimens, follow-up for oncology patients, hospital dentistry, and the dentist's role in cancer care.

Accomplishments: Presently, several areas receive support from the grant. The clinical program is carried out at the Philadelphia VA under the supervision of Drs. Dodson, Reiter, Kent and Samit. Approximately 2-3 students rotate through the VA every two weeks. During the first 5 months of the program the students have seen approximately 250 patients receiving a wide variety of anti-cancer therapy. We have developed a seminar series consisting of eight hours during the second year in which the differential diagnosis of neoplasms and neoplastic-like diseases of the head-and-neck are discussed. The seminar groups are composed of approximately 20 students each in order to maximize the learning experience. Each case is presented as an unknown and the diagnosis will be made by the students. Secondly, four hours of new lecture time will be instituted into the second year pathology curriculum. A cancer manual is nearing completion; it covers etiology and epidemiology of head-and-neck cancer, relevant anatomy, staging and selected topics. Patients with suspicious lesions are referred to the oncology clinic which meets every Wednesday afternoon. This clinic helps to establish proper lines of referral for the dental students.

Plans: Upcoming plans include: (1) evaluation of the program's effectiveness both from the student's and faculty perspectives; (2) expanding the Oncology clinic to three days a week; (3) development of a summer rotation for at least 2 students; and (4) presentation of a continuing education program for general dentists.

Program Director: Margaret H. Edwards, M.D.

From 09/01/80 - 05/31/83

FY 81: \$71,333

Dr. Thomas H. Staniscic, University of Arizona, School of Medicine, Tucson, Arizona

Objectives: The principal objective of our research is to use clonal assay techniques to accurately determine in vitro sensitivity of individual bladder tumors to specific anticancer drugs and to correlate in vitro/in vivo response to these agents. A successful effort would facilitate individualized chemotherapy for bladder cancer patients with agents chosen on a predictive basis. A secondary goal is to correlate the in vitro biologic characteristics of clonogenic urothelial cells with the in vivo clinical behavior of the urothelium. Studies of the clonogenicity, karyotype and colony morphology of clonogenic cells may assist in the diagnosis of bladder cancer and the identification of prognostic markers.

Accomplishments: To date, 28 bladder tumors have been successfully cloned in agar and 22 have demonstrated sufficient colony growth (30+/plate) to permit drug testing. Ninety-four laboratory drug exposures have been performed, 71 at concentrations achievable systematically in vivo. In only 7 cases has in vitro drug exposure reduced colony survival to 35% of that seen in untreated controls. Three of these instances involved Phase I and II agents (interferon, cisretinoic acid, anthracenedicarboxaldehyde) and 4 involved standard agents (adriamycin 2, thiotepa, mitomycin). Because of this observed in vitro tumor resistance to standard agents, we are now routinely screening investigational drugs in the laboratory. In vitro/in vivo systemic and intravesical drug treatment correlative trials are underway and we have successfully treated our first patient with a systemic agent (anthracenedicarboxaldehyde) on a predictive basis, achieving > 75% reduction in a bulky abdominal metastasis. Five patients with CIS have also been treated with intravesical thiotepa and/or mitomycin on a predictive basis. Four of 5 are stable or have reverted to "atypia" on cytology and/or biopsy after treatment, and in this group colony survival after in vitro drug exposure has ranged from 30-54%. One patient has progressed to invasive disease despite intravesical treatment with both thiotepa and mitomycin, but colony survival after in vitro exposure to both agents was 95-100% of untreated controls. In another 91 patient study of individuals with non-neoplastic "suspicious" and neoplastic bladders, we have confirmed our previous finding that urothelial cells from these groups exhibit a differential capacity to clone in agar.

Plans: Over the next two years we will attempt to enter 20-30 patients/per year into a systemic drug treatment protocol correlating in vitro/in vivo response. Five patients/year will enter a similar intravesical treatment protocol. We will place increased emphasis on screening Phase I and II agents in vitro and on chromosomal studies of clonogenic cells.

Program Director: William E. Straile, Ph.D.

Publications:

Buick, R.N., Staniscic, T.H., Fry, S.E., Salmon, S.E., Trent, J.M., Krasovich, P.: Development of an Agar/methylcellulose Clonogenic Assay for Cells in Transitional Cell Carcinoma of the Human Bladder. Cancer Research 39: 5051-5056, 1979. (In Press when Grant Submitted).

Staniscic, T.H., Buick, R.N.: An In Vitro Clonal Assay for Bladder Cancer: Clinical Correlation with the Status of the Urothelium in 33 Patients. J. Urol. 124: 30-33, 1980. (In Press when Grant Submitted).

Staniscic, T.H., Buick, R.N. Salmon, S.E.: Soft Agar/Methylcellulose Assay for Human Bladder Carcinoma in Salmon, S.E., (ed.): Cloning of Human Tumor Stem Cells, New York, Alan R. Liss, Inc. 1980, (pp. 75-83).

Staniscic, T.H., Buick, R.N., Trent, J.M., Fry, S.E., Salmon, S.E.: In Vitro Clonal Assay for Bladder Cancer: Studies of the Biologic Potential of the Urothelium and Determination of In Vitro Sensitivity to Cytotoxic Agents. Surgical Forum 31: 585-587, 1980.

Staniscic, T.H., Buick, R.N., Trent, J.M., Fry, S.E., Salmon, S.E.: An In Vitro Clonal Assay for Bladder Cancer: Studies of the Biologic Potential of the Urothelium and Determination of In Vitro Sensitivity to Cytotoxic Agents. J. Surg. Oncol., Accepted for Publication.

Grant 28505: The Coping Strategies of 600 Women After a Mastectomy

From 09/01/80 to 09/01/81

FY 81: 0 (Ann. \$103,226)

Dr. Theresa F. Rogers, Columbia University, New York, New York 10027

Objectives: The purpose of this research is to analyze the coping strategies used by women recovering from a mastectomy; determine which ones are effective in reducing stress and improving recovery; and identify the types of women who use effective coping strategies and those who do not. Data for this research are available from a study conducted with previous support from the National Cancer Institute. Analysis of coping strategies focuses on structural variables (age, race, ethnicity, income, education, and stage in the life cycle), contextual variables (conditions of the situation itself); and social interaction (specifically, affiliation--contact with another woman who has a mastectomy). The usefulness of coping strategies will be assessed in terms of reducing emotional distress and facilitating return to usual activities and social roles.

Accomplishments:

1. Two literature reviews have been undertaken. The first concerns theoretical and empirical work published on various coping strategies, their efficacy and their relationship to personal characteristics. The second focuses on the recovery experiences of mastectomy patients as presented in empirical and non-empirical sources;
2. Affiliation is being assessed in part from patient data and in part from interviews with 50 volunteers who visit mastectomy patients in the hospital. In addition, the directors of Reach to Recovery programs in the counties represented in the survey of mastectomy patients have been contacted about the organization of their respective programs and the recruitment and training of volunteers.
3. Two questionnaires have been developed, one for interviewing county directors of Reach to Recovery, and another for volunteers.
4. Data files from the original data set have been reconstituted for this study of coping strategies. The data were collected in one-hour interviews with 652 mastectomy patients between 29 and 65 years of age, without distant metastases, who reside in 17 contiguous counties in southeastern New York and who underwent surgery between May 1978 and January 1979. Analysis is underway to identify relationships between structural characteristics and the use of various coping strategies.
5. As a result of the two literature reviews and preliminary data and analysis, a new codebook has been developed and responses from a random subsample of 200 mastectomy patients have been recoded to identify coping strategies that were not included in the original preparation of the data.

Program Director: Sandra M. Levy

Plans: Analysis will begin shortly on the efficacy of different coping strategies--specifically, the extent to which they may reduce emotional distress and facilitate return to usual activities. Then, the kinds of strategies that patients report will be compared to those that volunteers recommend to test the hypothesis that peer-support efforts assist patient recovery by sharing effective coping strategies.

From 07/01/80 to 03/31/82

FY 81: \$108,335

Dr. John H. Edmonson, Mayo Foundation

200 First Street S.W., Rochester, MN 55901

Objectives: This is a plan for study and assessment and further development of cancer education for medical students, residents, and advanced oncologic trainees. We plan (1) to identify specific cancer education objectives for each training level, (2) to assess our current success in accomplishing these objectives, and (3) to determine what is being taught at each level more globally. Following these studies we will define any improvements needed and introduce any modifications required in current curricula and programs. We will evaluate this program on a continuing basis attempting to assess our accomplishments over time.

Accomplishments: During the first nine months of grant support the following activities have been provided: (1) Oncology Department Core Curriculum, (2) Weekly Oncology Conference, (3) Medical School Oncology Lectures, (4) Oncology Society. Much of the initial year funding has provided support for our efforts to define cancer education objectives in a comprehensive form for each level of education (medical graduate, residency graduates, and subspecialty oncologic traineeship graduate).

Plans: As described above, we will complete the identification of cancer education objectives and then proceed with the task of assessing how well these objectives are being met and determining globally what is currently being taught at each level.

Program Director: Margaret H. Edwards, M.D.

Grant 28603: Clinical Cancer Education Program
From 07/01/80 to 06/30/83 FY 81: \$30,128
Dr. John R. Benfield, City of Hope National Medical Center,
1500 East Duarte Road, Duarte, California 91010

Objectives: The objective of this project is to test the hypothesis that specific application of the classic tutorial method will be successful in developing personal self-education skills in surgical oncology trainees.

Accomplishments: An unforeseen obstacle was the lack of suitable instructional material to prepare faculty for their role in the tutorial program. A training manual for faculty is in the final stage of preparation.

A comprehensive matrix for tutorial topic selection has been organized. This permits ready assignment of a topic sufficiently limited for tutorial purposes, while retaining the capacity to provide breadth of coverage over a series of tutorials.

A structure for Divisional Grand Rounds has been developed which permits useful inter-relationships between the tutorial system training and the traditional clinical grand rounds presentation format.

Program evaluation questionnaires are being validated prior to controlled multiple-evaluator testing in real situations.

Plans: To begin operation of the tutorial system as the involved faculty members complete the needed orientation.

To continue development of Clinical Cancer Education activities beyond the Division of Surgery, in collaboration of the ongoing institutional Continuing Medical Education program.

Program Director: Margaret H. Edwards

From 09/30/80 to 05/31/83

FY 81: \$74,978

Dr. M. Eric Gershwin, Department of Internal Medicine, University of California, School of Medicine, Davis, California 95616

Objectives: The NB rat is an inbred strain initially developed by Dr. R.L. Noble in Vancouver, B.C. characterized by susceptibility to both spontaneous and androgen induced prostate neoplasia. This model is now widely used with major attention focused on chemotherapy. However, there has been only a paucity of attention directed at identification of tumor specific antigens in these tumors. Because NB rat prostate tumors have been maintained by serial passage for multiple generations, without major alterations with respect to histology, hormone receptors, or biologic behavior, it is believed that this is an ideal system to generate monoclonal antibodies directed against tumor specific antigens. Accordingly, using both mouse/mouse as well as mouse/rat hybrid systems, animals transplanted with NB rat neoplasia are being screened and cloned for generation of antibody to specific prostate tumor markers.

Accomplishments: The major direction of our work is being directed at improved methods for screening cloned hybridoma supernatants and optimal regimens to generate high titer antibody responsiveness. Preliminary work performed thus far indicates that both enzyme linked immunoassay as well as radioimmune assay (using Fab2 antisera) is a reliable and reproducible system. Direct subcutaneous transplantation, as opposed to tissue mincing or cell membrane preparations, appears to be the best means for generating antibodies. The system is being studied in parallel in both NB rats, inbred Fisher rats, as well as BALB/c mice.

Plan: It is our hope to generate a series of clones which produce antibody against tumor specific antigens in NB rat prostate neoplasia. These antigens would then be serially quantitated in aging animals and levels monitored in a variety of organs and tissue fluids. Finally the ability of these reagents to characterize tumor natural history will be determined.

Publications: None.

Program Director: Andrew Chiarodo, Ph.D.

Grant 28715: Experimental Chemotherapeutics of Pancreatic Cancer

From 09/01/80 to 05/31/83

FY 81: \$46,715

Dr. Barbara K. Chang, Medical College of Georgia, Augusta, Georgia 30912

Objectives: The overall objective of this project is to investigate the relationship between the tissue uptake and distribution chemotherapeutic agents by the pancreas and pancreatic adenocarcinoma and the antitumor activity of these agents. Two animal pancreatic ductal adenocarcinoma models have been chosen to carry out the project in inbred Syrian golden hamsters. The models have been developed and supplied by Drs. D.G. Scarpelli and M.S. Rao, Department of Pathology, Northwestern University and include: (1) the well-differentiated pancreatic adenocarcinoma (WD PaCa) which is a carcinogen-induced solid tumor model passaged subcutaneously (s.c.) or surgically implanted, and (2) the poorly-differentiated pancreatic adenocarcinoma (PD PaCa), which is a spontaneously-arising, ascitic model passaged by intraperitoneal (i.p.) injection. The ultimate goal of this project is to provide information that would lead to more rational and informed clinical trials and to provide a basis for the understanding of the sensitivity and/or resistance of pancreatic cancer to chemotherapy.

Accomplishments: To date, the pharmacologic studies have focused upon Adriamycin (doxorubicin; ADR). Significant findings include a very high uptake of ADR in the normal pancreas of both hamsters and rats. ADR levels achieved in the WD PaCa were quite low compared to normal hamster pancreas or PD PaCa, which had intermediate ADR levels. These differences in ADR uptake may partly explain the differences in sensitivity to ADR between the WD PaCa, which is relatively resistant to ADR, and the PD PaCa, which is sensitive to ADR. Drug sensitivity studies are currently being conducted both in vivo and in vitro (via clonogenic assays).

In vivo studies have shown that the WD PaCa is relatively resistant to ADR (at 2 dose levels), 5-fluorouracil, vincristine, methotrexate, cyclophosphamide, actinomycin D, and mitomycin C. PD PaCa is sensitive in vivo to ADR, but not to mitomycin C, nor Streptozotocin. For ADR and mitomycin C, good correlation of the in vitro and in vivo sensitivity has been found for both tumor models.

Plans: Drug uptake studies in the coming year will include methotrexate (MTX) and actinomycin D. Since MTX (conventional dose) was relatively ineffective against WD PaCa in vivo, high dose MTX with leucovorin rescue will be attempted. Antitumor drug testing will be expanded to include other agents, including some experimental drugs, and combinations of agents. Further comparison of in vivo and in vitro drug response will be carried out. If the correlation holds, future preliminary screening may be more efficiently performed in vitro.

Program Director: William E. Straile, Ph.D.

From: 08/01/80 to 04/30/83

FY 81: \$77,725

Dr. Eileen A. Friedman, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue,
New York, NY 10021

Objective: The objective is the study of tumor progression in the human colon by:
1) developing tissue culture techniques to culture premalignant epithelial cells from benign tumors (adenomas); and, 2) identifying a set of phenotypic markers to distinguish premalignant epithelial cells from benign tumors with low malignant potential from those with a high tendency to become cancerous.

Accomplishments: A tissue culture method has been developed to routinely obtain primary cultures of premalignant epithelial cells from tubular, villotubular, and villous adenomas. The cultures are free of fibroblasts and display characteristic epithelial structures such as functional complexes (tight junctions, gap junctions, and desmosomes) and a brush border as shown by electron microscopy. Culture cells are able to transport water and salts as shown by their formation of hemi-cysts or domes (out-pocketings of the monolayer which remain one-cell thick) due to the vectorial transport of H_2O . Domes are characteristic of transporting epithelium. Epithelial cultures of 10^3 cells remain viable for 8 weeks. A high and, therefore, representative proportion of each adenoma class has been cultured: 29 of 34 tubular adenomas (85%), 19 of 22 villotubular adenomas (86%), and 18 of 21 villous adenomas (86%). Under my culture conditions, epithelial cells from the tubular adenomas are stimulated to replicate by added epidermal growth factor while cells from the more advanced adenomas are not. This is the first phenotypic marker which distinguished premalignant cell populations. Other phenotypic markers include response to the endogenous tumor-enhancing compound, deoxycholic acid; response to phorbol ester tumor promoters; secretion of a plasminogen activator; and expression of a fetal-specific cytoplasmic antigen. Cells from different types of benign tumors exhibit different patterns of expression of these markers.

Plans: The major aim is to test whether phorbol ester tumor promoters, which cause cell clustering, disruption of gap junctions, and release of a plasminogen activator from only late stage or advanced premalignant cells, fully transform these cells and make them become capable of tumor formation in nude mice and/or growth in soft agar.

Publication:

Friedman, E. et al.: "Tissue Culture of Human Epithelial Cells from Benign Colonic Tumors". In Vitro, in press, 1980.

Program Director: Vincent J. Cairoli, Ph.D.

Grant 28846: Renovation of Clinical Cancer Research Outpatient Facility,
Columbia University

From 06/81 to 05/85

FY 81: \$426,938

Dr. Sol Spiegelman, Director, Cancer Center, Institute of Cancer Research,
Columbia University, New York, New York.

Objectives: Renovation of existing space to build an outpatient clinic
for the Comprehensive Cancer Center. The outpatient clinical research
unit is headed by Dr. Rose Ruth Ellison.

The renovation project will enable accomplishment of the following
cancer research programs:

1. Drs. Grump, Lo Gerfo, Kister, Chang, Tretter, Perloff and Spiegelman -
Breast Cancer Program will evaluate prognostic factors in mastectomy
patients.
2. Dr. Olsson - Other Solid Tumor Program will evaluate the combination
of drugs in several organs.
3. Drs. Ellison, Halper and Rapoport - Lymphoma Program will interface
with basic and clinical programs.

Accomplishments: The preliminary design objective and cost estimate were
completed in September 1980. The peer review reduced the size of the
project from 11,960 net square feet to 8,278 net square feet. A re-
design will therefore be required. The design will be completed by
June 1982; it will be reviewed by NCI Research Facilities Branch for
compliance with grant, biohazard safety, and facility safety criteria.

Plans: a) Complete design by June 1982.
b) Accomplish remodeling by December 1984.
c) Begin research in remodeled facilities.

Program Director: Donald G. Fox, Ph.D.

Grant 28847: Efficacy Studies of Diagnostic X-Ray Examinations

From 05/01/80 to 12/31/83

FY 81: \$175,664 (estimated)

Dr. Herbert L. Abrams, Peter Bent Brigham Hospital, Division of Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115

Objectives: This study seeks to determine prospectively the frequency of specific indications for the upper gastrointestinal series (UGI) and the intravenous pyelogram (IVP), the yield of important abnormalities associated with these indications, the sensitivity and specificity of the UGI and the IVP, and the diagnostic loss, economic gain, and radiation decrease associated with the restricted set of indications. These objectives will be attained and compared in three settings: a teaching hospital, a community hospital, and a health maintenance organization. In all three, a series of forms will be prospectively completed by the referring physician, the examining radiologist, and the research assistant, which will detail the indications and pertinent data, record the radiologic diagnosis, and include the clinical and pathologic follow-up and verification. Data will be stored in the computer for a two-year period and analyzed during the third. An optimal strategy for clinical use of UGI and IVP will be designed so as to minimize cost and radiation exposure with the least possible loss of important diagnostic information.

Accomplishments: By March, 1981, all of the preliminary groundwork for this study had been completed, and the body of the research is now well underway. Preliminary data on test indications and results for the UGI series have been obtained from each of the three participating institutions and have been tabulated by computer. Our first report showed the results of 685 UGI examinations (253 from the teaching hospital, 317 from the community hospital, 125 from the health maintenance organization). These results were generated according to the various reasons submitted by physicians for ordering the tests -- e.g., abdominal pain, nausea, diarrhea, and low hematocrit. The frequency of each indication and percentage of the total cases examined were tabulated. In turn, radiologic results for each of the indications were themselves divided into five categories, according to the radiologist's degree of certainty that an abnormality was present; that is, each indication was broken down to show how many patients were found to have each of the following categories of radiologic results: 1) no abnormality, 2) unlikely abnormality, 3) possible abnormality, 4) probable abnormality, 5) definite abnormality. At all institutions, the most frequently listed indication for UGI examination was abdominal pain. Positive results occurred most often with indication of hematemesis. In 28 patients who had hematemesis as an indication, 19 (68%) were found to have either a probable or a definite abnormality. Our preliminary results suggest that an accurate assessment of potential high-yield examinations will be possible after data have been collected on approximately 800 additional patients.

Plans: Plans for the coming year include follow-up data on patients having UGI's and the start and completion of the study involving intravenous pyelograms. Further efforts will be directed towards resolving differences in physician compliance at the three health care institutions.

Program Director: Dorothy R. Brodie, M.D.

Grant 28860: Interferon: Effects on Immunity to Bladder Tumors

From 09/30/80 - 5/31/83

FY 81: \$82,061

Dr. Timothy L. Ratliff, Department of Surgery/Urology, Washington University
School of Medicine at the Jewish Hospital of St. Louis, 216 South Kingshighway
St. Louis, Missouri 63110

Objectives: The objectives of this proposal are to evaluate the effects of gamma (immune) interferon (IFN_{γ}) on cell-mediated immune responses in vivo and in vitro and to determine the efficacy of IFN_{γ} , as an antitumor agent. To this end, we propose to examine the effects of IFN_{γ} , leukocyte (IFN_{γ}) and varying percentages of both on the following: (1) natural killer cell activity (NK), antibody-dependent cell-mediated cytotoxicity (ADCC) and the generation of cytotoxic T lymphocytes (CTL) in vitro for both human and murine lymphocytes; (2) antitumor activity using the transplantable transitional cell carcinoma, MBT-2, in C3H/He mice; (3) NK, ADCC and CTL activity during tumor therapy will be correlated with anti-tumor activity.

Accomplishments: The utility of protein A from Staphylococcus aureus (SpA) as an IFN_{γ} inducer was examined. Specific antibody neutralization studies showed conclusively that IFN_{γ} is produced after SpA stimulation. Dose-response experiments showed donor-to-donor variation in the concentration of SpA required for maximum IFN_{γ} production although SpA at 50 ug/ml consistently induced IFN_{γ} titers at or near peak values. Time-course studies showed that peak IFN_{γ} titers appeared 24 hours after SpA treatment.

Further studies performed to maximize IFN_{γ} production revealed that lymphocyte concentrations of $2-5 \times 10^6$ /ml provided maximum IFN_{γ} yields. Moreover, IFN_{γ} - containing supernatants could be harvested for 3 successive days by removing supernatants and adding fresh medium to stimulated lymphocytes, thus providing substantially increased yields of IFN_{γ} .

Preliminary cell fractionation studies suggest that SpA, unlike other IFN_{γ} inducers, stimulates IFN_{γ} production by nonadherent lymphocytes that lack high affinity receptors for sheep erythrocytes but express Fc receptors for I G.

Plans: Our research goals for the coming year are as follows: (1) to complete our studies related to identifying the lymphocyte subpopulation(s) responsible for SpA-induced IFN_{γ} production, (2) to study in more detail the modulatory effects of IFN_{γ} on Nk, ADCC and CTL activity, (3) to partially purify both human and murine IFN_{γ} , (4) to begin therapy studies on the MBT-2 transitional cell carcinoma in C3H/He mice.

Publications:

Ratliff, T.L., McCool, R.E., and Catalona, W.J.: Interferon Induction and Augmentation of NK Activity by Staphylococcus Protein A. Cell Immunol. 57:1-12, 1981.

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Catalona, W.J., Ratliff, T.L. and McCool, R.E.: Induction of Gamma Interferon and Augmentation of Natural Killing and Antibody-dependent cell-mediated cytotoxicity by Protein A from Staphylococcus Aureus. Nature (In Press).

Grant 28874: Bladder Cancer Model: Aid for Planning and Evaluation

From 09/01/80 to 05/31/82

FY 81: \$72,648 (est.)

R. E. Greenfield, M.D., St. Vincent Hospital, Worcester, Massachusetts

Objectives: A mathematical model has been developed as an aid in synthesizing currently available research information, in testing the logic and implication of hypotheses about different aspects of bladder cancer, and in making programmatic decisions. In most planning and decision-making situations, the human mind cannot systematically give adequate consideration to all relevant factors. As a result, subjective judgments and available objective data for only a few intuitively selected factors are considered. Because of the multiplicity of relevant factors and associated uncertainties, computerization is necessary if modeling is to be comprehensive and yet practical. It allows quick response to differences or changes in intuitive judgment.

Accomplishments: To provide a practical analytical aid for addressing bladder cancer in humans, it was necessary for the modeling effort to include all aspects of the bladder cancer problem: development of the disease; screening, diagnosis, and therapeutic interventions; post-treatment disease persistence or recurrence; follow-up, etc. Thus, the problem was broken down into these separate components and each was represented as a distinct system submodel.

The model system treats the sequence of events involved in the induction and progression of the disease and the attempts at its arrest as follows: (1) The disease submodel represents the induction and morphological status of the disease within the host up until the time of its detection, either as the result of a screening program or because the disease has progressed to the point where it has become symptomatic and clinical attention is sought; (2) the diagnosis and classification submodel represents the intervention activities undertaken to uncover and classify the existing disease for treatment; (3) the therapy submodel is a representation of the various therapeutic options available for the treatment of disease. After treatment, which results in the "stabilization" (if not cure) of the disease process, the status of the disease within the host is represented by (4) the cancer patient disease model.

An interactive cycle of treatment followed by disease recurrence continues until the disease has progressed to the point at which final treatment has been administered (where palliative interventions directed toward improving the quality of life rather than disease eradication are the only real options remaining) and the possibility of the host eventually succumbing to the disease exists. Of course, this sequence of events will not always terminate in death due to the cancer. At any time during this process, death from other causes may terminate the course of events.

Plans: Obviously, model inputs for validation studies concerning survival must necessarily be reflective of past intervention methods and efficacies. Upon validation of the model for the disease process using historical data or clinical management, the emphasis can shift to utilizing the model as a tool for predicting the consequences associated with proposed changes in the intervention strategies. Recognizing that the basic inputs to the model have not been adequately validated at the writing of this abstract, a review of selected

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applications of the model will, nevertheless, be projected. Illustrative analyses of screening and treatment issues will be reviewed. The purpose of these computer exercises is to demonstrate the potential of the model and its flexibility in being able to address a wide spectrum of intervention issues. The specific results will be used as the vehicle for illustrating the model but will not be considered sufficiently firm to influence planning or intervention decision making.

Grant 28943: Case-control Study of Diet and Prostate Cancer in Hawaii

From 09/01/80 to 05/31/83

FY 81: \$121,809

Dr. Laurence N. Kolonel, University of Hawaii, 1236 Lauhala Street, Honolulu, Hawaii 96813

Objectives: This project will examine the role of diet in the etiology of prostate cancer. This subject has been little studied until now, and the dietary heterogeneity of Hawaii's multiethnic population offers a special opportunity for such research. Three separate components of the diet are being studied for their potential roles in the etiology of prostate cancer: (1) fats, (2) vitamin A and its precursors, and (3) zinc in relation to cadmium. The hypotheses being tested, which are based on both epidemiologic and animal data, are that high fat and cadmium relative-to-zinc intakes are risk factors for the disease, while vitamin A may be protective.

Accomplishments: This is a case-control study, based on histologically-confirmed prostate cancer patients from the five main ethnic groups in Hawaii, and matched neighborhood controls. Two controls are selected by a random-digit-dialing procedure for each case. Subjects are interviewed at home by trained interviewers regarding their quantitative intakes of a wide variety of food items representing the major sources of the components of interest. The interview also includes smoking, alcohol, occupational and medical histories. In addition, a sample of hair is collected for trace element assay in the laboratory.

The study is still in its first year of funding. To date, a combined total of more than 150 cases and controls have been interviewed. The laboratory procedures for cadmium and zinc analysis, using atomic absorption spectrophotometry, have been developed and testing of hair samples has begun.

Plans: During the course of this 3-year project, we plan to interview 500 cases and 1000 controls. Repeat interviews will be conducted on a small proportion of the subjects to test for reproducibility. Intakes of the various food components will be computed from the diet histories and these will be compared between cases and controls. The cadmium and zinc content of the hair samples will be correlated with the findings from the food histories.

Publications: None.

Program Director: Andrew Chiarodo, Ph.D.

Grant CA 29023: Exploratory Grant for Cancer Control at Cancer Centers

From 09/01/80 to 08/31/83

FY 81: \$399,917 est.

John R. F. Ingall, M.D., Comprehensive Cancer Center of Metropolitan Detroit, 110 East Warren Avenue, Detroit, Michigan 48201

Objectives: The aim of the project is to expand and extend the Comprehensive Cancer Center's affiliations and collaborative inter-organizational relationships throughout the State of Michigan. A statewide master plan of cancer control is to be developed. Cross-fertilization of ideas, a sharing of resources, and collaborative, cooperative efforts both at controlling the disease and understanding it better are expected byproducts of these outreach efforts. The program also includes a developmental fund of \$50,000 a year which is to be used to launch worthwhile new cancer control activities.

Accomplishments: During the first year of the grant the following projects were initiated with the help of developmental funds:

1. The Human Lymphocyte Antibody (HLA) Program, which will develop a 5,000 person file of HLA-typed blood donors and which will benefit cancer patients with severe marrow depression incident to intensive chemotherapy; and
2. The School of Health Education Pilot Project, which will enhance the capability of teachers to effectively meet both the cognitive and affective learning goals of their students in regard to smoking and cancer issues.

The cancer control outreach sponsored by this grant played a major role in the following beneficial developments in our region:

Hospice Programs: The planning and negotiations which led to the establishment of Hospice of Southeastern Michigan, Inc., were assisted by Dr. John Ingall. In addition to his continued support to this program, he chairs a task force which is designing a study on the quality of life for Hospice patients around the State.

Oncology Education for Professionals: In conjunction with this outreach program, three professional education seminars have been conducted by Wayne State University. Three more symposiums are in the planning stage. Conferences on marijuana therapy and pain treatment have been initiated by Dr. Ingall. Physicians throughout the State have participated in these seminars.

Consultative Support of Local Programs: Consultative support has been given to the leadership of a community-wide Hospital Oncology Program in Flint and the hospital cancer programs in Marquette. Written and verbal contacts have been made with Area Hospital Councils throughout the State to explore potential cancer control developments. The Outreach staff has also retained and augmented existing relationships with the Community Hospital Oncology Program in Grand Rapids and with oncology groups around the State.

Plans: The following plans have been set for the second year of this program:

1. To continue the ongoing cancer control outreach activities;
2. To further develop and implement the cancer control outreach master plan;
3. To complete and evaluate the School Health Education Pilot Projects; and
4. To continue professional oncology programs. Sponsorship of seven symposiums is anticipated for next year.

Publications: To date there have been no publications resulting from this project.

Grant 29320: Gonadal, Behavioral, and EEG Correlates of Smoking

From 07/01/80 to 06/30/82 FY 81: \$90,790 (estimated)
Dr. Edward L. Klaiber, The Worcester Foundation for Experimental
Biology, Inc., Shrewsbury, Massachusetts 01545

Objectives: This research project proposes to establish that there are gonadal and central nervous system (CNS) parameters which significantly differentiate young adult male smokers from nonsmokers. Preliminary studies indicated that smoking was associated with certain gonadal abnormalities (testicular varicoceles, low sperm count, reduced sperm motility, and sparse pubic hair development, suggesting a low level of testosterone stimulation). In addition, cognitive and electro-encephalographic indices known to be sensitive to testosterone administration also differentiate smokers from nonsmokers. These differences are more pronounced in smokers who started smoking during early adolescence (early onset), as opposed to individuals who started smoking in late adolescence (late onset). This implies that the most detrimental effects of smoking are seen when the onset of smoking occurs during an early critical stage of physical and mental development.

The following are the goals for this study over the two-year grant period:

- o To evaluate in 150 smokers and 150 nonsmokers the relationship of smoking status, age of onset of smoking, and duration of smoking to the following gonadal and CNS variables: incidence of testicular varicoceles, seminal fluid indices, pubic hair development, the Automatization Cognitive Style, and EEG "driving" response to photo stimulation.
- o Since some of the gonadal and CNS abnormalities suggest decreased testosterone stimulation in smokers, blood metabolic clearance and production rates of testosterone will be measured in 20 early onset smokers, 20 late onset smokers, and 40 nonsmokers.
- o The data collected in Goal 1 will be assessed by means of factor analyses and by examination of correlation matrices. Strong identified factors will be submitted to multivariate regression to evaluate association between identified gonadal-CNS factors, and age, smoking status, time of onset of smoking, and duration of smoking

Accomplishments: Studies have been completed in 150 of the 300 required subjects during the first year. Thirty-two of the required 80 subjects have had testosterone metabolic clearance and production rates determined. The data base currently is too small to meaningfully carry out the full battery of statistical analyses identified in Goal 3. However, a partial analysis of the data collected to date is supportive of our preliminary study. The following project-related publication reported an increased incidence of testicular varicoceles in smokers: Klaiber, E.L., Broverman, D.M., and Vogel, W.: Increased Incidence of Testicular Varicoceles in Cigarette Smokers, Fertil, Steril. 34: 64-65, 1980.

Plans: During the next year, the required number of subjects will be studied to fulfill Goals 1 and 2. When the data base is complete, the

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appropriate statistical procedures listed in Goal 3 will be undertaken with the assistance of two epidemiological consultants. If the findings of our preliminary study can be confirmed, a new area of medical risk, involving impaired gonadal and CNS function associated with smoking, will have been defined.

From 09/01/80 to 08/31/82 FY 81: \$16,218 (estimated)
Dr. Kenneth E. Friend, Clarkson College of Technology, Potsdam,
New York 13676

Objectives: Cigarette smoking provides several sorts of stimulation (nicotine itself, activities surrounding smoking, passage of smoke into the lungs), and various theories of smoking behavior include stimulation as one of the motives contributing to smoking. There appear to be stable individual personality differences in the motive to seek out intense stimulation--"need for stimulation" (nStim). Important relationships between measures of nStim and smoking have been observed, with those "high" in nStim smoking more and beginning at an earlier age than the "lows." Measures of nStim include, but are not limited to, questionnaire assessment. For example, another successful measure has determined the tendency of the nervous system to augment or reduce the perceived psychological impact of stimuli. This work has supported the theory that one aspect of individual differences in nStim is perceptual augmentation/reduction. Reducers seek higher levels of objective stimulation in order to achieve the same pleasing internal state that augmenters achieve with less intense objective stimulation because reducers' nervous systems dampen the impact of stimuli. Several studies suggest that, perhaps through adaptation, continual exposure to intense environments (e.g., an "intense," noisy urban environment) tends to increase reduction and hence, increase nStim; similarly, short-or-long-run experiences of lower stimulation may lower nStim. The objective of this research is to identify children at higher risk of smoking due to intense environmental stimulation and/or personality, and it will indicate what steps can be taken to alleviate adverse effects of these factors.

Accomplishments: Survey data from 314 college freshmen (17 to 19 age range) were collected within three months of their arrival at college. Questionnaire and non-questionnaire measures of nStim were obtained as well as personality data from the Eysenck Personality Inventory; extensive background information relating to complexity, novelty, and intensity of environment during the childhood years was also collected; and, of course, reports of smoking behavior (frequency, age when first started, contexts where smoking is most likely to occur) and of other substance usage patterns (e.g., beer and other alcohol usage, coffee drinking, marijuana and other illicit drug usage) were obtained.

Computer files have been constructed with 56 pieces of information for each subject. Preliminary data analyses investigating two issues have been run: correlations among proposed nStim measures were investigated, and relations of this trait to substance usage patterns were examined. Several expected relations among the nStim measures were found, although the non-questionnaire measures seem to measure a different facet of the trait than is indicated by the paper-and-pencil measure. In any case, both kinds of measures show substantial and significant relations to substance usage patterns generally and to smoking in particular. These preliminary results have been reported recently at a professional meeting. The results are

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encouraging and useful because, in part, they are from a slightly younger group than much of the other research in the literature--the key difference here is that this is a group where there has been no long-term influence from the college environment and, thus, there is more chance to see childhood and adolescent environmental influences.

Plans: A large number of analyses still remain to be done on the data from Study I. These include analyses related to characterizing the intensity of childhood environments and relating this to nStim differences and to substance usage patterns. Additionally, the data are sufficiently complete to allow investigation of additional interesting issues such as the degree of relationship and types of patterns that characterize use of various substances as well as factors that predict the age when smoking started.

Also, an experiment is in progress designed to provide (1) evidence on the possible influence of environmental stimulation on nStim and smoking (this time via experimental rather than correlational data) and (2) to further indicate whether relaxation or other procedures which alter environmental stimulation levels may have any use in decreasing--even on a short-run basis--substance usage and smoking patterns. Sixty college students identified as smokers and 60 identified as nonsmokers will participate in the study. There are three conditions: (a) a "neutral" condition where subjects read a book for 30 minutes, (b) a relaxation condition in which they are taught and practice a progressive muscular relaxant technique for 30 minutes, and (c) a stimulating condition where they play games and listen to loud rock music for 30 minutes. Various questionnaire and non-questionnaire data are being collected before and after the experimental condition. These include nStim measures (which, among other things, include self-reports of interests in various types of substance usage). Two unobtrusive measures of preferences for stimulating substances have been included: (a) while completing the final set of questionnaires, subjects are asked whether they would like coffee or apple juice to drink; (b) all smokers are asked to bring cigarettes and to smoke one during completion of the first set of questionnaires--if they initiate smoking again during the second set, this is noted by the experimenter. The rationale for studying both smokers and non-smokers is that it is useful to know whether reactions to the experimental treatments differ between these groups and, also, because eventual applications of reduced sensory input techniques may also apply to smoking prevention among nonsmokers.

Grant CA 29354: Exploratory Grant for Cancer Control at Mayo Comprehensive Cancer Center

From 07/11/80 to 06/30/83 FY 81: \$362,799 est.
Dr. David Ahmann, Mayo Foundation, 200 First Street
Rochester, Minnesota 55901

Objectives: Mayo intends to serve as a focus and catalyst for cancer care programs in the local community and region, having been convinced that a devotion to local and regional needs is essential to sustain the viability of the Mayo Comprehensive Cancer Center. We also, with previous experience, have been led to believe that involving the community and region can provide invaluable assets for clinical research and symptomatic supportive care and for the accurate evaluation of the impact of the Comprehensive Cancer Center on the quality of cancer patient care delivery. Because of Mayo's unique setting in a largely rural area, our relationship with the community and region, and the large number of patients served, we believe are ideally situated to develop model programs which can be subjected to meaningful evaluation in the regional setting, particularly through the North Central Cancer Treatment Group which has many activities implemented through the Comprehensive Cancer Center.

Accomplishments: Although just recently granted, the Cancer Control Project has initiated the following programs:

1. Implementation of a Hospice Support Program for patients within the tri-county area surrounding Rochester, Minnesota. The implementation of this program followed a Needs Assessment and Resource Survey of involved cancer patients and their families prior to death. A data base has been accumulated prior to intervention and it is our intention to reassess the situation following our intervention to see whether or not the needs of these patients have been met. This program does have this applicability to regional centers particularly in the rural setting.
2. Almost completed has been a Cancer Patient Needs Assessment on a large group of patients chosen by random selection who enter the Comprehensive Cancer Center for comprehensive cancer care. A broad ranged structured interview getting prospective data will allow us to project meaningful intervention for this group of patients. This program, as well, would have its applicability to other centers within our region in an effort to assure comprehensive cancer patient care.
3. A survey has been obtained from the North Central Cancer Treatment Group Project Directors with respect to the needs as they see them within their given communities. Particularly prominent in this survey were the needs these investigators felt for patient and professional educational programs organized through the Comprehensive Cancer Center. We intend to follow through with meaningful projects with built-in evaluation techniques.
4. Since the Cancer Information Service had made video tapes for cancer information within the State of Minnesota and had gathered some demographic data prior to the implementation, we chose to do projects within the two Dakotas as well. Using pre- and post-intervention knowledge assessment

Program Director: Carlos E. Caban, Ph.D.

techniques, we will attempt to ascertain what improvement in basic cancer knowledge may have occurred through these public service broadcasts sponsored by the Comprehensive Cancer Center.

5. We have been fortunate in acquiring the services of Mr. Michael Roach who will be our Program Evaluator. Shortly to arrive is our cancer patient and professional Educational Specialist and we will begin to be able to implement educational programs more formally, particularly with respect to evaluation techniques.

Plans: The Mayo Comprehensive Cancer Center has changed its administrative function with an ongoing Cancer Control Committee responsible to the Center Executive Committee and in charge of cancer control activities. It has been our intent that many committees appointed by the Cancer Control Committee will be ad hoc committees project oriented and specialized in scope with respect to specific problems identified. An example is the objective assessment currently ongoing of patients' needs for supportive services. We are going to also assess and address the rehabilitation needs of patients with selective cancers. Educational programs for both professionals, paraprofessionals and patients will be shortly be shortly implemented. All of the implementation envisioned will be preceded by evaluation and followed after intervention for impact of proposed programs.

Grant 29383: Monoclonal Antibodies to Pancreatic Tumor Markers

From 09/30/80 to 05/31/82

FY 81: \$79,320

Dr. Herbert Z. Kupchik, Department of Microbiology, Boston University School of Medicine, 80 E. Concord Street, Boston, Massachusetts 02118

Objectives: The overall long-term goal of this project is to develop a clinically useful diagnostic test for pancreatic cancer in asymptomatic patients. The successful achievement of this goal centers on the belief that unique macromolecules are synthesized and shed by tumor cells. These macromolecules would gain access to the circulation where they could be detected and quantitated by *in vitro* assays. Monoclonal antibodies will be produced by fusion of mouse myeloma cells with splenic lymphocytes from mice immunized with encapsulated, viable, human pancreatic cancer cells. The antibodies will be used to isolate macromolecules shed by tumor cells *in vitro*. These reagents will provide the foundation for future development of clinical assays.

Accomplishments: Human pancreatic cancer cells were found to survive prolonged encapsulation in alginate gel pellets. Preliminary experiments suggest that variations among different cancer cell lines cause some to grow and escape the gel while others remain relatively dormant while continuing to release cell surface markers (e.g., CEA) through the gel. Studies are underway to determine to what extent increased gel concentrations can affect the growth of cells and/or shedding of marker.

COLO 357 pancreatic cancer cells when encapsulated in one percent alginate did not increase in number but remained viable for at least 45 days in culture and continued to shed CEA into the medium. These cells also survived encapsulation for five months when the pellet was subcutaneously implanted in a mouse from which the spleen was subsequently removed for fusion with mouse myeloma cells. The resulting hybridomas are currently being screened for antibodies to cell surface components. PANC-1 pancreatic cancer cells which do increase in number and escape the one percent alginate pellet have also been used as encapsulated immunogens and the spleen of one such immunized mouse has been fused. These resulting hybridomas are also being screened for antibody production. We anticipate that we will have several monoclonal antibodies to both shed and cell surface bound tumor macromolecules, and will have begun isolation and characterization of these markers by September, 1981.

Plans: We plan to continue the search for and production of monoclonal antibodies specific for human pancreatic cancer. These antibodies will be used in turn to identify and isolate pancreatic cancer specific macromolecules. The specific antibodies and macromolecules (antigens) will then be incorporated into assays to be evaluated for clinical usefulness.

Program Director: William E. Straile, Ph.D.

Grant 29479: Informal Self-Help Approaches to Smoking Cessation

From 05/15/80 to 05/14/83

FY 81: \$66,211

Dr. Arthur J. Garvey, Veterans Administration Outpatient Clinic,
Boston, Massachusetts 02108 and Harvard School of Dental Medicine,
Boston, Massachusetts 02115

Objectives: The purpose of this research project is to investigate the strategies of individuals who successfully quit smoking cigarettes using their own initiatives. We plan to: (1) obtain and classify the types of self-help strategies employed by subjects who quit smoking on their own; (2) compare and contrast these strategies with strategies used by recidivists (those who tried to quit smoking but failed); (3) relate personal characteristics such as age, motivation for quitting, degree of addiction, and personality both to strategies employed and to the probability of successful quitting; and (4) compare the relative importance to successful quitting of strategies employed versus the importance of personal characteristics.

Accomplishments: Months 1-6 of the current year were spent identifying and scheduling interviews for a pool of eligible former smokers and recidivists from the 1,370 subjects who returned a smoking status update questionnaire. A group of 300 recidivists and 300 age-matched quitters were randomly selected for the study. From this group of 600 subjects, approximately 400 agreed to participate in our study. Interviews and personality testing began around month 7; the first 30 individuals were used to pre-test and refine the structured interview and personality instruments. To date, 185 subjects have been interviewed and tested. Numerical coding schemes have been developed for open-ended interview questions, and questionnaire and interview data on approximately 100 subjects have already been transferred to numerical data recording forms, keypunched, verified, and stored on IBM cards and magnetic tape files. Each subject has 9 IBM cards of information, corresponding to approximately 300 variables measured on him.

Plans: Year 2 of the project will be devoted to the completion of the second half of our interviews and personality assessments, construction of the final portion of our computerized data files, and the statistical analysis of our data. Specific goals are the following: (1) determination of the major strategies used by successful quitters and the strategies used by recidivists; (2) examination of the similarities and differences in the strategies used by quitters and recidivists; (3) inspection of possible differences in reasons for quitting, personality traits, social supports, motivation, degree of addiction and other variables between quitters and recidivists who used the same strategy; (4) examination of possible differences in personality, age, and other characteristics between successful quitters who used different strategies; and (5) initial study of the importance to successful quitting of personal traits like motivation, addiction, and personality compared to the importance of strategies employed.

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From 09/30/80 to 05/31/83

FY 81: \$57,452

Dr. David V. Gold, Division of Experimental Pathology, Department of Pathology,
University of Kentucky Medical Center, 800 Rose Street, Lexington, Kentucky
40536

Objectives: The objectives of this project are to purify and characterize by immunologic, physical and chemical means a human pancreatic duct tissue specific antigen and to evaluate the potential of the antigen as a marker for pancreatic disease and in particular pancreatic cancer.

Accomplishments: For our initial studies on antigen purification, we have utilized normal adult pancreas. Employing an antigen purification scheme previously developed for the isolation of colonic mucins (phenolwater extraction followed by fractional ethanol precipitation, treatment with nucleases and molecular sieve chromatography) we have obtained a pancreatic mucin fraction which by immunoelectrophoresis and disc gel electrophoresis appears homogeneous. A single precipitin arc was noted in immunoelectrophoresis (having a mobility in the α_2 region) when a rabbit anti-pancreatic tissue antiserum was employed. No precipitin arcs were observed when a rabbit anti-normal human serum antisera was employed. By disc gel electrophoresis (SDS with 2 mercaptoethanol), a single band excluded from a 7.5% polyacrylamide gel was noted when stained by Coomassie blue for protein or the PAS method for carbohydrate. To date, this mucin fraction (PDA) has been purified from five different normal adult pancreatic specimens. Yields of purified antigen ranged from 0.019 to 0.05% (by weight). Actual weight of antigen purified ranged from 3.5 to 19.5 mg. Purification of antigen from two other normal adult pancreas specimens is in progress. Antisera are currently being prepared in rabbits by immunization with purified PDA from three individual specimens.

Plans: We plan to continue purification of PDA from normal adult pancreas and from xenografts of human pancreatic cancer grown in athymic nude mice. When purification is considered complete, as determined by immunoelectrophoresis and disc gel electrophoresis, we will begin analysis of physiochemical properties. Production of antisera will continue, as we begin an immunohistochemical analysis to determine the distribution of PDA in normal and neoplastic tissues. A radio-immunoassay and/or ELISA procedures will be developed for the detection of PDA in the body fluids of patients.

Program Director: William E. Straile, Ph.D.

Grant 29514: Cell Lines From Human Pancreas and Biliary Carcinomas

From 09/01/80 to 05/31/83

FY 81: \$42,986

George E. Moore, M.D., Ph.D., Department of Surgery, Division of Surgical Oncology, Denver General Hospital, 750 Cherokee Street, Denver, Colorado 80204

Objectives: The objectives of this project are: (1) to establish and characterize new human tumor cell lines derived from pancreatic and biliary tract carcinomas, and (2) to make these well-characterized cell lines available to other qualified investigators. The objectives for this project year were: (1) to solicit primary pancreatic and biliary tract tumor specimens and/or solid and ascitic metastases, (2) to establish these specimens in continuous culture, (3) to characterize resultant cell lines, (4) to characterize previously established cell lines of pancreas and biliary tract carcinomas, and (5) to make available to other investigators these cell lines.

Accomplishments: During the project year, 16 surgeons and 10 pathologists in the Denver Metropolitan area and in the Colorado region and participating members of the National Pancreatic Cancer Project were contacted and asked to participate in procuring sterile biopsy and ascitic fluid specimens from patients with carcinomas of the pancreas, gallbladder, and biliary tract. Characterization of RPMI 7451, a cholangiocarcinoma cell line, was undertaken. RPMI 7451 was characterized on isozyme profile, steroid hormone receptors, secretion of CEA, ultraand phase morphology, and karyology. COLO 357, pancreatic carcinoma, COLO 346, gallbladder carcinoma, and RPMI 7451, cholangiocarcinoma were tested for growth in serum-free medium using GEM 1717 medium base supplemented with 10% Hespan (Hetastarch 1.2% v/v). COLO 357, COLO 346, and RPMI 7451 maintained cell viability and typical morphology for up to 14 days. LvP, a pancreatic adenocarcinoma cell line established by S. G. Gordon at the University of Colorado Health Science Center, was tested for secretion of pancreatic enzymes. LvP secretes elastase and trypsin (2.09 µg/ml and 0.36 µg/ml respectively). No chymotrypsin activity was detected. During this project period, 28 requests for COLO 357 were received and honored (19 from within the United States and 9 from abroad). COLO 357 COLO 346, RPMI 7451, and LvP were maintained in continuous culture in our cell bank and subcultures of each cell line were frozen every two weeks and maintained in our frozen cell bank. The well-characterized cell lines provided by the studies in this proposal will facilitate other investigators' studies of human pancreatic and biliary tract carcinomas.

Plans: This research proposal for the coming year will concentrate on: (1) initiating and establishing cultures of pancreatic and biliary tract carcinomas, (2) characterizing the two cell lines, LvP and RPMI 7451, and submitting appropriate manuscripts for publication, (3) continuing to maintain the already established cell lines of pancreas and biliary tract carcinomas, (4) making these cell lines available to qualified investigators, and (5) publishing reports of these cell lines in the scientific literature.

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Publications:

Morgan, R. T., Woods, L. K., Moore, G. E., Quinn, L. A., McGavran, L., and Gordon, S. G.: Human cell line (COLO 357) of metastatic pancreatic adenocarcinoma. Int. J. Cancer, 25:591-598, 1980.

Morgan, R. T., Woods, L. K., Moore, G. E., McGarvan, L., Quinn, L. A., and Semple, T. U.: A human gallbladder adenocarcinoma cell line. In Vitro (In press), 1981.

Grant 29518: ^{125}I , 5FU, and External Radiotherapy for Pancreatic Cancer

From 05/01/79 to 06/30/82

FY 81: \$44,504

Ralph R. Dobelbower, M.D., Medical College of Ohio, Toledo, Ohio 43699

Objectives: The major objectives of this research project are to test the feasibility toxicity and efficacy of combination therapy (systemic 5-FU, precision high dose external beam radiation therapy, and ^{125}I seed implantation) for unresectable adenocarcinoma of the exocrine pancreas.

Accomplishments: Between June 1979 and May 1981, eight patients were entered on study, four females and four males ranging in age from 55 to 75 years. Four patients had stage II disease, two patients stage III disease, and two patients had stage IV disease (minimal hepatic metastasis). All patients underwent at least one exploratory laparotomy and all patients had biliary and gastrointestinal bypasses performed. All patients had implantation of radioactive ^{125}I seeds into the pancreatic neoplasm. The total number of seeds per patient varied from 30 to 120 seeds. One patient with Barlow's syndrome expired suddenly two weeks after the operative procedure and received neither precision high dose external beam therapy nor systemic chemotherapy.

The remaining seven patients received (or are now awaiting) external beam radiation therapy delivered by a linear accelerator or a betatron. Two patients were treated with 45 MEV photons, two with 15 MEV photons and three with 10 MEV photons. One patient with stage IV disease received only 2100 rad PHD external beam therapy, as his course was progressively downhill. This patient received adjuvant 5-FU on the first three days of his PHD external beam therapy. One patient is recuperating from ^{125}I implantation and awaits PHD external beam therapy. The remaining four patients received external beam radiotherapy doses ranging from 4100 rad to 6300 rad. One of these received adjuvant 5-FU during the first of three days of his course of external beam therapy and refused further chemotherapy after the completion of PHD external beam therapy. Another patient received no systemic therapy post PHD radiation because of a progressive downhill course. A third patient received no systemic therapy because of the development of a massive hepatic cyst during the course of her external beam radiotherapy. This patient was also found to have pleural metastatic disease. Two patients are currently alive at two and 21 months post diagnosis. These two patients have no clinical evidence of recurrent disease.

The small number of patients entered on study thus far precludes a definitive statement regarding the toxicity or efficacy of this particular combination of modalities. It is expected that case accession will increase during the ensuing year.

The initially proposed external beam radiation therapy dose delivery protocol was modified shortly after the beginning of the study to allow the delivery of a single dose of 500 rad before implantation of ^{125}I seeds. This modification was made initially because of Shipley's implant data in which he found a 75 percent incidence of distant metastasis as compared to only 33 percent in the precision high dose external beam study. It was postulated that the act of transgressing the tumor bulk with needles for implantation of seeds might

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actually disseminate tumor. The single dose of 500 rad was based on the extrapolation from the Princess Margaret Hospital rectal study in which a single preoperative dose of this magnitude was shown to significantly reduce local recurrence and enhance survival in patients with Duke's stage C carcinoma of the rectum. The present protocol calls for the administration of a single dose of 500 rad prior to implantation for all patients for whom a histologic diagnosis of adenocarcinoma of the pancreas is established prior to laparotomy for implantation.

Plans: We plan a modification of the ^{125}I seed application to make the process of ^{125}I seed implantation into the pancreas more facile and the applicator less cumbersome.

Publications:

Dobelbower, R.R.: Current radiotherapeutic approaches to pancreatic cancer. Cancer 47:1729-1733, 1981.

Dobelbower, R.R., Borgelt, B.B., Strubler, K.A., Kutcher, G.J. and Suntharalingam, N.: Precision radiotherapy for cancer of the pancreas: technique and results. Int. J. Radiation Oncology Biol. Phys., 6:1127-1133, 1980.

Grant 29525: Transformation In Vitro of Human Urinary Tract Cells

From 09/30/80 to 05/31/83

FY 81: est. \$69,946

Dr. C.A. Reznikoff, Department of Human Oncology, University of Wisconsin, Madison, Wisconsin 53792

Objectives: The primary objectives of this project are: (1) to establish cultures of human transitional epithelium from embryonic bladder and postnatal ureter obtained from surgery, (2) to identify and characterize these cells by phase contrast microscopy, and by scanning and transmission electron microscopy (SEM and TEM) at each stage of adaptation to tissue culture, and (3) to perform mutation and transformation experiments on suitable cultures using bladder specific carcinogens. Because of the difficulties encountered in culturing urothelial cells, there is a particular emphasis in the first year of this project on empirically determining which culture conditions will optimize the growth of human urothelial cells in vitro (e.g. choice of media and substrate, addition of growth factors, hormones or polyamines, and the use of irradiated feeder layers).

Accomplishments: The outgrowth of urothelial cells from over 200 randomly distributed explants ($<1 \text{ mm}^2$ each) of embryonic bladder was studied using different media combinations. The percent of explants showing growth of urothelial cells was compared. In these experiments explants were placed in P60 plastic petri dishes. The best growth was observed in explants cultured in Waymouth MB 756/1 media supplemented with 7% fetal calf serum, 1 unit/ml insulin, 5 ug/ml hydrocortisone, 5 ug/ml transferin, and 10 ng/ml epidermal growth factor (EGF). In this group, as compared to explants grown in other media, the greatest fraction of explants showed growth (35/50), growth was observed earliest (66% by day 4), the average size of the colonies was largest at 10 days (approximately 15 mm in diameter), and these dishes were confluent at 3 weeks. Phase contrast photographs of living cells at each stage of adaptation to culture have been taken and SEM and TEM studies of representation cells are in progress.

Using the media described above, a cell culture has been derived from bladder barbotage of a patient with Grade III transitional cell carcinoma. These cells are being fully characterized. SEM and TEM studies are in progress and tests to determine growth of cells in soft agar, and the ability of cells to form tumors in nude mice are underway. Chromosome analysis will be done. We will document any changes in behavior or fine structure which occur in vitro. We hope to use these cells as a prototype of transformed human urothelium and will compare their behavior in culture with normal urothelial cells.

Plans: We have attained excellent growth of primary explants of human embryonic urothelial cells. However, optimal means of passing cells to new dishes have not been defined. We will investigate the best technique of dispersion of cells for transfer using different mechanical and enzymatic methods. We will also determine the usefulness of altering the substrate to increase viability and colony forming ability of passaged cells. Different substrates to be tested include collagen, fibronectin, and the extracellular matrix (ECM) of human endothelial cells derived from ureter. Irradiated feeder layers of various cell strains will be used to enhance growth.

Program Director: William E. Straile, Ph.D.

After culture conditions are optimized, transformation and mutation experiments will be performed on both explant cultures and bona fide strains of urothelial cells using bladder specific carcinogens, such as 2-naphthylhydroxyamine, and N-methyl-N-nitrosourea.

Publications:

Resnikoff, C.A., and DeMars, R.: In Vitro Chemical Mutagenesis and Viral Transformation of a Human Endothelial Cell Strain. Cancer Research 41: 1114-11126. 1981.

Grant 29526: Clonal Properties of Human Bladder Cancer

From 04/01/81 to 05/31/83

FY 81: est. \$74,200

I.F. Tannock, Princess Margaret Hospital and Ontario Cancer Institute, Toronto, Ontario, Canada

Objectives: We propose to study and compare the clonal properties of human bladder cancer implanted into semi-solid culture and immune-deprived mice, and to seek clinical correlation of these properties with the course of the disease. We describe preliminary experiments performed up to initiation of funding by the National Bladder Cancer Project.

Accomplishments: Cell suspensions from biopsies of bladder tumors of 22 patients were plated (5×10^5 cells/plate in semi-solid culture using both a 2-layer agar method, or an agar-methylcellulose method (Buick et al., Cancer 39:5051, 1979). Colonies were generated from 13/22 patients with a mean plating efficiency of 3.6×10^{-4} .

Conventional CBA mice were rendered immune-suppressed by thymectomy at four weeks followed by sequential Cytosine Arabinoside and Whole Body Irradiation (Steel et al., Br. J. Cancer 37:224, 1978). Five of 20 biopsies from human bladder cancer have grown or are growing progressively in these mice and, contrary to experience with nude mice, histological evidence of metastases in lungs and/or liver has been found in mice bearing three xenografts. Histologic examination of xenografts is consistent with anaplastic transitional cell carcinoma. The two patients whose biopsies have generated in vitro colonies as well as primary growth and metastases of xenografts have had a rapidly fatal course.

In order to study methods for improving the success of xenografting, we have implanted four established cell lines of human bladder cancer into immune-deprived mice with or without further manipulation, and into nude mice. All of the lines grow progressively from implants of 10^5 cells or more in immune-deprived CBA mice (but not nude mice), and at least three of them metastasize to liver and lungs in immune-deprived CBA mice. Administration of sheep anti-mouse lymphocyte serum decreases the number of cells required to generate tumors for the two lines that have been tested, but there was no effect of steroids.

Plans: Experiments are underway (1) to relate success of xenografting with immunologic measures such as T-cell and NK-cell activity, and (2) to develop a xenograft lung colony assay which may be compared with the in vitro method for studying clonal properties of human bladder cancer.

Program Director: William E. Straile, Ph.D.

Grant 29543: Cancer in Women Receiving Exogenous Estrogen

From 09/30/79 to 07/31/82

FY 81: \$123,217 (Estimated)

Dr. M. Arnold, University of Denver, 2199 South University Boulevard,
Denver, Colorado, 80208

Objectives: The original objective of this project, to demonstrate a model surveillance and follow-up system for postmenopausal women taking hormones, has been revised as the environment surrounding the use of estrogen replacement therapy has changed. The objectives now are to ascertain what physicians in the Denver metropolitan area believe to be good clinical practice regarding estrogen replacement therapy, and to identify the influence of various sources of information on their practices.

Accomplishments: This past year has involved the development and design of an interview schedule for physicians. A pilot study of thirty-six physicians has been completed and the questionnaire revised based on this experience.

Plans: A controlled pretest will be carried out with emphasis on interviewer training, interview standardization, and coding uniformity. These activities are expected to be completed in June 1981. Immediately following the pretest a representative sample of physicians in the Denver metropolitan area will be interviewed. The first round of these interviews are expected to be completed by September 1981.

Concurrently, a study of prescription patterns in the Denver metropolitan area has been completed to ascertain the percentage of estrogen prescriptions written by the various medical specialties. Those proportions will be used to develop the representative sample of physicians in the Denver metropolitan area to be interviewed. An annotated bibliography is in preparation for distribution to the physicians who will be interviewed.

The final year of the project will involve completion of the interviews and data compilation and analysis. We expect to be able to identify the range of practice in the Denver metropolitan area regarding the use of estrogen replacement therapy and factors influencing its use.

Program Director: Andrew F. Hegyeli, D.V.M., Ph.D

Grant 29558: Smoking Prevention and Youth: Motivational Strategies
(Project RAY:S - Risk and Youth: Smoking)

From 09/30/80 to 09/30/82

FY 81: \$137,679

Dr. Martin V. Covington, Department of Psychology and
Dr. Carol N. D'Onofrio, School of Public Health through the
Lawrence Hall of Science, University of California at Berkeley,
Berkeley, California 94720

Objectives: The overall objective of this research is to develop effective, widely applicable educational interventions which will increase the ability of young people to make informed decisions about their behavior in situations that tempt them to smoke or to engage in other activities potentially injurious to their health. Fundamental to the design of effective interventions is a more sophisticated understanding of psychosocial and situational variables that influence smoking and non-smoking behavior among youth. A related objective therefore is the development of a theoretical model of smoking uptake which fits empirical data on the functions that smoking may serve for young people confronting common developmental tasks. Findings are expected to have both theoretical and practical implications for preventing and/or limiting other high-risk, self-destructive behaviors. Investigation focuses upon sixth and eighth graders as key target groups for prevention.

Accomplishments: The first project year is divided into two interlocking phases of basic research. During six months of exploratory work, over 800 young people representing a wide range of socioeconomic and ethnic groups were studied in school and community settings to (1) identify the dimensions and dynamics of decision-making and beliefs in situations which place youth at risk of smoking, and (2) develop instruments to assess individual differences associated with smoking or non-smoking behavior in these situations. Projective techniques in both English and Spanish, personal and group interviews, and formal questionnaires in the two languages, as well as retrospective data about the circumstances of smoking initiation collected from young adults, consistently reveal that although youth are able to identify specific health disadvantages related to cigarette smoking, they do not consider smoking to be a significant social or personal health issue. Rather, the act of smoking for children is basically an instrumental means of dealing with non-smoking issues that confront the adolescent on a daily basis. Moreover, cigarettes as objects have an astounding range of uses. Fourteen categories of motives for smoking have been discerned. Significant differences in factors affecting smoking decisions were found by sex and grade level. Furthermore, major differences in the formal qualities of thought (e.g., complexity, realism, extremity of consequences, concrete vs. abstract reasoning, and use of role expectation) have been found in smokers' and non-smokers' reasoning about interpersonal dilemmas. Ethnic and social class differences were associated with fewer variations in smoking circumstances and motives; however, the differences found may be extremely important in developing effective anti-smoking interventions. These factors will be studied more formally during the second six months of the 01 project year; a pilot survey of some

Program Director: Catherine S. Bell, M.S.

300 sixth and eighth graders will be conducted in spring 1981, followed by a formal survey of approximately 800 young people in fall. Development and testing of the theoretical model of smoking uptake progresses and is advanced by all aspects of field research.

Plans: The second project year will be devoted to the development of interactive educational interventions based on real-life choices about smoking commonly encountered by sixth and eighth graders. In the third year these materials will be field-tested and formally evaluated in 12 experimental classrooms and 12 control classrooms at each grade level.

Publications:

Covington, M.V.: Youth and Decision-making Dilemmas: New Approaches to Smoking Uptake and Prevention. In Proceedings of the 1981 International Seminar on School Health Education, in press.

Thier, H.D.: Teenagers and Beginning Smoking. In Proceedings of the 1981 International Seminar on School Health Education, in press.

From: 06/01/75 to 07/31/81 FY 81: -0- (Ann. \$57,803)
Dr. K.L. Yielding, University of South Alabama College of Medicine,
Mobile, AL 36688.

Objectives: The objectives are to study the details of deoxyribonucleic acid (DNA) damage and repair in colon cells and to determine the potential importance of repair and its regulation in carcinogenesis and genotoxic therapy. Resolution of a potential role for bile acids has been emphasized in these experiments due to earlier reports that lithocholic acid has a promoting effect on experimental colon tumors and the implications that bile acids were risk factors in human cancer. Damage to DNA and regulation of DNA repair by agents to which the colon may be exposed are highly significant to the understanding of colon cancer.

Accomplishments: Damage and repair of DNA following exposure of cultured cells to lithocholic acid was found to be a complex phenomenon requiring at least intact cell nuclei. DNA strand breaks were not produced in purified DNA or in freshly isolated nucleoids. Treated nuclei can be co-lysed with untreated nuclei, however, to produce damage in the latter. Ultrastructural studies by scanning electron microscopy (SEM) and transmission electron microscopy (TEM) reveal no evidence for generalized cell organelle damage following exposure to twice the level of lithocholic acid. No effects seen with the β -OH-analog of lithocholate or the 3 Cholenic acid.

DNA repair was studied in tissue culture cells and in freshly isolated colon mucosal cells by following the appearance of DNA strand breaks following damage by alkylating agents, x-ray or photoaffinity labeling by ethidium monoazide. These studies produced three important findings: 1) the rate limiting steps for repair are quite different for different insults, 2) simultaneous damage from two agents can act synergistically; and 3) photoaffinity labeling results in a special sensitivity of DNA to alkali induced strand breaks. Knowledge of such interactions between insults is essential to understanding cancer risk.

Plans: The kinetics and regulation of DNA damage and repair in colon cells following administration of colon carcinogens in conjunction with other DNA insults, especially lithocholic acid will be pursued. The lithocholic acid damage to DNA will be studied for specificity mechanisms and biological consequences.

Publications:

Kulkarni, M.S., Heideprim, P.M. and Yielding, K.L.: Production by Lithocholic Acid of DNA Strand Breaks in L1210 Cells. Cancer Res., 40:2666-2669, 1980.

Cantrell, C. and Yielding, K.L.: Binding of Ethidium Monoazide to the Chromatin in Human Lymphocytes. Biochem. Biophys. Acta, 609:173-179, 1980.

Program Director: Vincent J. Cairolì, Ph.D.

From 05/01/81 to 04/30/84 FY 81: \$254,431
Steven Paul Schinke, Ph.D., University of Washington, Seattle,
Washington 98195

Objectives: This research will evaluate self-control training to prevent young people from smoking cigarettes. Sixth graders will learn health information, problem solving, self-instructions, and interpersonal communication to help them avoid tobacco use. These youths will be compared to age-mates who get only health information and to youths who are only tested. A research design and multimodal measures will quantify the relative effects of self-control training, health information, and no training on youths' cigarette smoking knowledge, attitudes, and practices. Because of the research, new methods will be available for the primary prevention of tobacco's toll.

Accomplishments: From May 1, 1981, to September 30, 1981, the investigators achieved several goals. Collaboration with two school districts was formalized, and a cohort of sixth-grade women and men was recruited. After 350 young people and their parents or legal guardians consented to participate, 200 students were randomly selected. The young people were randomly placed in one of four conditions: pretest, information only, and posttest; pretest and posttest; and, posttest only.

Pretest data were checked for randomness. Youths' self-reported and physiological data were correlated with their interpersonal performance relative to cigarette smoking. Pilot research and the conceptual model behind self-control prevention training were written up, presented at a national conference, and accepted for publication in a professional, peer review journal.

Findings to date show a feasible and responsive project. The investigators encountered little difficulty during youth recruitment, parental consent, and pretesting. Analyses of pretest data establish consistent randomization and point to correlations for subsequent research. Illustrative are that demographic characteristics of sex, family background, and peer relationships skew youths' tobacco knowledge and attitudes. Similar to adults, young persons who are predisposed to smoke believe cigarettes are less harmful than do youths who lean away from smoking. Physiological data and self reported smoking significantly correlate for the majority of sixth graders tested. And, cognitive problem solving and overt interpersonal performance highly correspond with each other and with young people's attitudes and knowledge about cigarette smoking.

Plans: Self-control and information only training will be delivered to sixth-graders in respective conditions. All youths will be posttested and will turn in physiological data and self-reported smoking for all remaining years. Two cohorts of 500 sixth graders each will be tested, trained, retested, and followed.

Program Director: Catherine S. Bell, M.S.

Publications:

Schinke, S. P., and Blythe, B. J.: Cognitive-behavioral prevention of childrens' cigarette smoking. Child Behavior Therapy, in press.

Grant 29911: Relaxation Training to Reduce Averseness of Chemotherapy

From 05/01/81 to 05/01/84

FY 81: \$53,275

Patricia H. Cotanch, Ph.D., Duke University Medical Center, Durham
North Carolina 27710

Objectives: The study is evaluating the effectiveness of progressive muscle relaxation (PMR) in reducing anxiety nausea and vomiting in two groups of patients receiving chemotherapy. The first group are identified as experiencing refractory drug-induced nausea and vomiting in spite of aggressive use of standard antiemetics ("own" historical control design). The second group are patients who are beginning drug regimens that have a 50 percent chance of causing drug-induced nausea and vomiting not relieved by standard antiemetic therapy. These patients are randomized into Ex. group A (instructed in PMR) and C group B (instructed in placebo procedure). To date there is no published empirical investigation regarding the efficacy of PMR. If PMR procedures significant results in reducing drug induced nausea and vomiting, the technique can be easily taught to patients, allowing them to participate in their treatment and possibly improve confidence by making treatment more palliative.

Accomplishments: Not applicable, grant became operative May 1, 1981.

Plans: Year 01 - will concentrate on accruing patients in the 2 group study plan. Oncologist and oncology nurses have been notified that patient referrals can begin after June 1. The investigator has made contact with two other behavioral researchers in this area who are studying a similar clinical research topic, with the hope that a collaborative study can be done in the future.

Program Director: Sandra M. Levy, Ph.D.

Grant 29913 : Multidiscipline Approach to Psychosocial Cancer Care

From 05/01/81 to 04/31/85

FY 81: \$79,158

Jimmie Holland, M.D., Memorial Sloan-Kettering Cancer Center, New York, New York

Objectives: This three year project proposes to promote the development of psychosocial support programs for cancer patients at community general hospitals (those associated with the Regional Network Hospitals of Memorial Sloan-Kettering Cancer Center) by means of a workshop-tutorial consultation model. A multidiscipline group will develop educational materials, identify five interested consortium hospitals who will send a staff member to the workshop and flexible tutorial and offer consultation to the staff person as they set up and develop a specific psychosocial program(s) in their own hospital. The program will be evaluated and a teaching model developed for use by others.

Accomplishments:

The initial contacts have been made through the Cancer Control Office with the Network Hospital Coordinators who meet monthly. Dr. Holland and several staff members have given lectures and workshops at several hospitals who have expressed interest in participation. Several are interested in hospice development, program evaluation, and volunteer programs. The core staff will begin regular meetings in May to plan contact with hospital and the educational and evaluation materials.

Plans: The first workshop is planned for 1982, with five hospitals participating, followed by ongoing consultation with each hospital by a liaison staff person. The pilot workshop-tutorial will be evaluated and the revised program reported in 1983 for 10 hospitals, with the third year having developed an acceptable model for use by others.

Program Director , Sandra M. Levy, Ph.D.

Grant CA 29953: Exploratory Grant for Cancer Control

From 03/01/81 to 02/28/83

FY 81: \$353,556

Dr. R. N. Taub, Columbia University Comprehensive Cancer Center
701 West 168th Street, New York, N.Y. 10032

Objectives: Our objective is to implement a broad range of regional cancer control activities for patients in the New York and New Jersey service areas of Columbia University Comprehensive Cancer Center. Collaborative and reciprocal programs will be developed in the areas of supportive care in patient management; psychosocial aspects of patient care; continuing education in oncology; cancer prevention and public education in cancer.

Accomplishments: This grant has only recently begun; we have formed joint planning groups composed of health care personnel from hospitals, state health departments, community groups, and industry to estimate cancer control resources and needs in conjunction with a community advisory board. Tumor registry format and cancer patient management data are being linked between cancer control affiliated institutions and the State Registries of New York and New Jersey. An interinstitutional oncology nursing education consortium has been formed under the auspices of the Cancer Control Program. Inservice and exchange programs have been implemented. A series of conferences on supportive care of cancer patients are being inaugurated.

Collaborative programs in professional and public education, patient referral, and occupational health are being developed in the areas of occupational health and nutrition.

Demonstration projects are being developed in the areas of psychosocial support for oncology patients and staff, and crisis intervention for cancer patients and their families, in collaboration with the cancer adjustment program of the ACS in New Jersey. Another project involves comprehensive algorithms for standardized, computerized occupational histories in cancer patients.

Plans: During the current year we hope to widen the linkages among the hospitals in our demonstration network, and expand their collaborative efforts with community institutions and organizations. Several research projects involving psychosocial support of cancer patients and their families, smoking cessation, and nursing education will have begun implementation.

Program Director: Carlos E. Caban, Ph.D.

Grant 30181: Remodeling of Biology Laboratories in Braun Laboratory
Building, California Institute of Technology.

From 06/81 to 05/83

FY 81: \$374,530

Mr. David Morrisroe, Vice President for Business and Finance and Treasurer,
California Institute of Technology, Pasadena, California

Objectives: Renovation of existing space to build biology laboratories
for members of the Cancer Center which is headed by Dr. Lee Hood.

The renovation project will enable accomplishment of the following cancer
research programs:

1. Dr. C. Parker - Molecular genetics research centered on the mechanisms
of regulation of structural gene transcription in *Drosophila melanogaster*.
2. Dr. E. Lazarides - tumor biology research involving cellular
cyto - architecture.
3. Dr. I. Weissman - immunology research in T-cell differentiation
and receptors.

Accomplishments: The preliminary design objective and cost estimates
were completed in September, 1980. The peer review reduced the size
of the project from 13,299 net square feet to 8,710 net square feet. A
redesign will therefore be required.

Plans: a) Complete design by September 1981.
b) Accomplish renovation by June 1982.
c) Begin research.

Program Director: Donald G. Fox, Ph.D.

Grant 30191: Renovation of Immunology Laboratories in Health Science
Building, Northwestern University Cancer Center

From 06/81 to 05/83

FY 81: \$318,000

Dr. Nathaniel Berlin, Director, Cancer Center, Northwestern University,
Chicago, Illinois

Objectives: Renovation of existing space to build a biohazard containment suite for members of the Immunovirology Program of the Northwestern University Cancer Center. The Immunovirology program is headed by Dr. Philip Paterson.

The renovation project will enable accomplishment of the following cancer research programs:

1. Dr. Philip Paterson - studies on neurovirus infection, neuroantigens and on the role of virus in neuroautoimmune diseases.
2. Dr. Bayer Thimmappaya - studies in gene regulation using adenovirus, or some adenovirus SV₄₀ hybrids as model systems.

Accomplishments: The preliminary design objectives and cost estimates were completed in 1980. The peer review did not reduce the scope of the proposal; therefore, no redesign is required.

Plans: a) Award construction contract by July 1981.
b) Complete construction and occupy the facility by September 1982.
c) Begin research.

Program Director: Donald G. Fox, Ph.D.

Grant 30197: Remodeling of Experimental Therapeutics Division Space,
University of Rochester Cancer Center.

From 06/81 to 05/84

FY 81: \$316,560

Mr. David A. McBride, University of Rochester, Rochester, N.Y. 14642

Objectives: Renovation of existing space for members of the newly formed Experimental Therapeutics Division of the University of Rochester Cancer Center. The new division is directed by Dr. Robert M. Sutherland.

The renovation project will enable accomplishment of the following cancer research programs:

1. Dr. D. W. Seimann - investigation of combined modalities of radio-sensitizers and chemotherapeutic agents.
2. Dr. Peter J. Conroy - increased understanding of radiation sensitizer cytotoxicity toward different tumor cells.
3. Dr. Philip Rubin - develop predictive models for severe radiation effects in vital viscera (lung and bone marrow).
4. Dr. Elizabeth D. Woodward - long-term study of population which experienced irradiation for benign conditions (enlarged thymus gland, lymphoid hyperplasia of the nasopharynx, and acute post-partum mastitis) and breast-irradiated women.

Accomplishments: The preliminary design objectives and cost estimates were completed in September 1980. The peer review reduced the size of the renovation project from 4,591 net square feet to 3,433 net square feet. A redesign will therefore be required. The schematic design will be completed by September, 1981 and will be reviewed by the NCI Research Facilities Branch for compliance with the grant, biohazard safety, and laboratory safety criteria.

Plans: a) Complete design by May 1982.
b) Accomplish remodeling by July 1983.
c) Begin research.

Program Director: Donald G. Fox, Ph.D.

Grant 30223: Alterations for an Experimental Radiation Therapy Laboratory,
University of Washington School of Medicine

From 06/81 to 05/84

FY 81: \$558,503

Dr. Janet S. Rasey, Department of Radiation Oncology, University of Washington
School of Medicine, Seattle, Washington

Objectives: Renovation of existing space to build a research laboratory suite
for members of the Radiation Oncology Department which is headed by
Dr. Thomas Griffin.

The renovation project will enable accomplishment of the following
cancer research programs:

1. Dr. Janet Rasey - studies of three murine tumor systems after iso-effective doses of low and high ET radiation.
2. Dr. P. Mahler - studies of normal tissue radiobiology.
3. Support Laboratories and shared facilities.

Accomplishments: The preliminary design objectives and cost estimate were
completed in 1980. The peer review reduced the scope of the project from
4,060 n.s.f. to 2,847 n.s.f. A redesign will therefore be required. The
schematic design will be completed in September 1981 and will be reviewed
by the NCI Research Facilities Branch for compliance with grant, biohazard
safety criteria, and laboratory safety.

Plans: a) Complete design by May 1982.
b) Accomplish alterations by July 1983.
c) Begin research.

Program Director: Donald G. Fox, Ph.D.

Grant 30237: Antecedents of Adolescent Cigarette Smoking: A
Longitudinal Study of Urban Black Youth

From 08/01/81 to 07/31/82 FY 81: \$113,092 (estimated)
Ann F. Brunswick, Ph.D., Columbia University, New York, New York

Objectives: This is a study of causal factors in the onset of adolescent cigarette smoking. A prospective cohort design is being applied to data already collected from a community representative sample of non-Hispanic urban black youth. The sample (N=535) is about equally divided between males and females and was interviewed twice: first when they were aged 12-17, inclusive; and six to eight years later when they were aged 18-23, inclusive. Of the approximately 400 youths who were not smoking when studied initially, about half subsequently reported daily cigarette smoking. Sociocultural and socioeconomic background, school achievement, social influences, psychological well-being, health salience and health practices will be analyzed in a linear causal model to explain the onset of regular daily cigarette smoking.

Plans: Reliability testing of predictor variables will be completed. Gender specific regression analyses then will be undertaken to test the social, psychosocial, and health behavior/attitude antecedents of daily cigarette use. The resultant models also will be compared to those which predict the onset of illicit drug use in order to identify factors which are common to, and those which are distinct in, the onset of different substance use behaviors. Implications for smoking prevention will be given special attention.

Program Director: Catherine S. Bell, M.S.

Grant 30238: Renovation of Chemistry Laboratories in Pharmacy Building,
University of Arizona

From 06/81 to 05/84

FY 81: \$32,918

Dr. Jack R. Cole, Dean, College of Pharmacy, University of Arizona, Tucson,
Arizona

Objectives: Renovation of existing space to build laboratories for members
of the Synthetic Medicinal Chemistry Program which is headed by
Drs. W. A. Remers and K. H. Schram.

The renovation project will enable accomplishment of the following cancer
research programs:

1. Dr. W. A. Remers - studies in mitomycin and other active antitumor
compounds.
2. Dr. K. H. Schram - research to develop a procedure for profiling
the urinary excretion of modified nucleosides in patients with
various neoplasms.

Accomplishments: The preliminary design objectives and cost estimates were
completed in 1980. The peer review reduced the size of the total project
and a redesign will be required.

Plans: a) Complete design by June 1982.
b) Accomplish renovation by August 1983.
c) Begin research.

Program Director: Donald G. Fox, Ph.D.

Grant 30456: Patients' Responses to Cancer: A Psychosocial Analysis

From: 08/01/81 to 07/31/82 FY 81: \$48,020
Dr. Ruth McCorkle, University of Washington, School of Nursing, Seattle
Washington, 98195

Objectives: The objectives of this one year project are: (1) to complete a thorough analysis of existing data assessing psychosocial aspects of living with lung cancer; (2) to prepare publications describing this research; and (3) to plan an intervention study to verify and elaborate the descriptive findings. Structural equation models derived from explicit substantive hypotheses will be formulated and fit to these data with the LISREL IV Computer Program. A study to evaluate how modest psychosocial interventions can help patients deal with specific cancer problems, such as pain and social dependency, will be designed after interpreting the LISREL analysis. If found effective, we anticipate that the intervention techniques could be readily adapted by interested health care professionals for use with many kinds of cancer. To encourage other psychosocial cancer research, we plan to develop a manual for our battery of instruments with complete instructions and psychometric properties.

Accomplishments: Our present two year research project was designed to develop a valid and reliable methodology to determine how successfully patients cope with one of two chronic diseases (lung cancer or heart disease) and its consequences. One outcome of the grant is to contrast characteristics of patients who cope well with advanced disease with those patients who do not. The sample consists of 65 patients with a confirmed diagnosis of lung cancer and 65 patients with a confirmed diagnosis of myocardial infarction. Subjects were interviewed at two times: one month (T_1) and two months (T_2) after confirmation of initial diagnoses. Preliminary findings suggest cancer patients, although reporting more symptom distress and less support from family and friends, report significantly fewer concerns than myocardial infarction patients. Changes in both groups of patients occur one month later. Cancer patients, although citing improvements in pain symptoms (probably due to radiation schedules) and support from family and friends, report increased concerns and mood disturbance. Physical improvement in myocardial infarction patients one month later is indicated by decreased social dependency. This improvement is accompanied, however, by greater acknowledged recognition of disease implications and increased mood disturbance.

To summarize, objective disease-related conditions improve comparably for both kinds of patients between one and two months after diagnosis, yet both kinds of patients grow more disturbed. Whereas myocardial infarction patients acknowledge a possible source of this trend in increased awareness of disease implications, cancer patients do not. In the proposed study, the effect of awareness on the mood, concerns, and coping ability of cancer patients will be a central issue.

Program Director: Catherine S. Bell, M.S.

Grant 30941: Third World Conference on Cancer Pain

From 07/01/81 to 06/30/82

FY 81: \$12,400

Dr. John J. Bonica, University of Washington, Seattle, Washington 98195

Objectives: To contribute support to those sessions of the Third World Conference on Pain that deal specifically with pain in cancer.

Accomplishments: This conference should summarize current understanding of the incidence of pain in cancer and its sequellae, mechanisms and best approaches to treatment including assessment of most efficacious use of narcotic analgesics.

Plans: Same as accomplishments.

Publications: A formal publication will result from the Congress.

Program Director: Donald N. Buell, M.D.

Grant 31769: Monitoring for Cancer Risks

From 04/01/79 to 03/31/82

FY 81: 0 (Ann. \$106,816)

Dr. J. Berg, Environmental Studies Program, AMC Cancer Research Center, 6401 West Colfax Avenue, Lakewood, Colorado 80214

Objectives: The overall objectives are (1) to create a computer-based system for the continuous monitoring of cancer registry data for the appearance of excess numbers of previously uncommon or rare cancer, and (2) to study the epidemiology of such cancers found in Colorado during the creation and testing of the program.

New environmental carcinogens can produce "new" types of cancer, e.g., asbestos and mesothelioma. Repeated searching registry data for such new events requires a computer, but past and current coding of cancer site and type requires major modifications before all examples of one cancer type are properly grouped together.

Accomplishments: Common coding schemes were created for cancer site and type so that old and new registry data would have formally equivalent codes. This has required over 100 changes in the code numbers from the 1968 Manual of Tumor Nomenclature and Coding and over 250 changes in the current International Classification of Diseases for Oncology. This recoding has been computerized so that it will be done automatically as part of the automated analysis.

Programs also have been created to divide registry data into appropriate groupings for monitoring. For instance, all connective tissue cancers are brought together whether they have been coded to the retroperitoneal area ("digestive system" in current coding), mediastinum ("respiratory system"), thorax and abdomen ("ill-defined site") or connective tissues of thorax and abdomen ("connective tissue"). The few cancers such as mesothelioma that are best grouped together regardless of site of origin have been identified and so treated.

Programs have been written to study this recoded data to discover statistically significant increases in (a) cancer of the young or early middle aged, (b) cancers of specific subsites such as renal pelvis or nasal sinuses, and (c) cancers of specific histology within an appropriate grouping such as hemangiosarcomas of the liver or adenocarcinoma of the vagina.

Plans: Study is underway of a much more difficult problem: which cancers of a site with different names and different code numbers are really different epidemiologically and which really are the same and deserve grouping for proper evaluation. A data base of about 800,000 cancer cases has been assembled and a scheme for semi-automated analysis is being tested.

To determine a feasible strategy for follow-up of computer-signaled cancer increases, an interview instrument has been developed for indepth probing of

Program Director: Dorothy R. Brodie, M.D.

familial, life-style, occupational and other environmental exposures. Interviews have been conducted covering rare cancer types.

Publications:

Berg, J. W. and Lampe, J. G.: High risk factors in gynecologic cancer. Cancer, "in press," 1981.

Berg, J. W., Percy, C. and Horm, J. W.: Recent changes in the pattern of occurrence of oat cell carcinoma of the lung: Trends in Cancer Incidence (Magnus, K., Ed.), Hemisphere Publishing-McGraw Hill, "in press."

Breast Cancer Detection Demonstration Project

From 03/73 to 02/81

FY 81: \$0 (Ann. \$2,524,000)

Objectives: The Breast Cancer Detection Demonstration Project was designed to demonstrate to the medical profession and to the public the application of periodic screenings in the detection of early breast cancer. Funds were provided by NCI contracts and ACS grants. Twenty-seven projects supporting 29 BCDDP screening centers were established in selected cities throughout the United States. At the completion of recruitment, the entire Project enrolled 280,152 women 35-74 years of age.

The goal of the Breast Cancer Detection Demonstration Project (BCDDP) was to increase awareness of breast cancer through the demonstration of methods and techniques for early detection. It was designed to demonstrate the use of breast screening modalities such as thermography, mammography, and physical examination in large scale screening programs. Education of the public and the medical profession in the methods of recruitment application of screening modalities, and follow-up of individuals referred to the medical community for consultation was of prime concern. In each project, approximately 10,000 women were enrolled over a two-year period. Each project provided up to five annual screenings for each woman who remained fully active in the program. Sreenees were recruited from the population at large, and an emphasis was placed on efforts to recruit a cross section of races, ethnic groups, and socio-economic levels, utilizing the volunteer corps of the ACS to the maximum extent. There was no charge to sreenees.

<u>Con</u> <u>tract #</u>	<u>Start</u>	<u>End</u>	<u>FY 80</u>	<u>Annual</u>	<u>PI/Organization</u>
45065	2/74	2/81	0	\$219,000	Bernard Fisher, M.D. University of Pittsburgh
45049	3/74	2/81	0	\$238,000	Barbara Threatt, M.D. University of Michigan
45067	2/74	2/81	0	\$219,000	Donald Young, M.D. Iowa Lutheran Hospital
45064	2/74	12/80	0	\$262,000	Robert McLelland, M.D. Duke University
55097	10/74	1/81	0	\$242,000	Arthur Present, M.D. University of Arizona
45098	6/74	2/81	0	\$214,000	Lewis Guiss, M.D. University of California, Los Angles
45095	6/74	1/81	0	\$267,000	Ned Rodes, M.D. Cancer Research Center

Project Officer: Richard D. Costlow, Ph.D.

45088	6/74	2/81	0	\$211,000	Morton Goodman, M.D. Good Samaritan Hospital
45096	5/74	1/81	0	\$210,000	Herbert Constantine, M.D. Rhode Island Hospital
55099	7/74	2/81	0	\$202,000	Dee Ingram, M.D. Vanderbilt University
55100	10/74	1/81	0	\$240,000	John Martin, M.D. St. Joseph's Hospital

Accomplishments: As of March 1, 1981, the contracts for the Breast Cancer Detection Demonstration Projects have expired and a long-term follow-up of selected screening participants has been implemented. From the start through March of 1980 more than 1.1 million screening examinations have been performed and more than 63 percent of the women enrolled have completed a fifth-year visit. Of the total surgeries performed, 4,333 were reported as breast cancer, and 33,981 were reported as benign biopsies or aspirations. In keeping with encouragement to continue a facility for breast cancer screening when federal funding ceases, 13 of the 29 centers have established a breast cancer screening service available with varied means of support such as fee for service and/or state or local support. As each Project closed, the participating women and their physicians were apprised of their status and were given information packets containing cancer information service numbers, brochures, leaflets on breast self examination and other information pertaining to a long-term follow-up in which they might be selected to participate. Over the project period, exposure to radiation from mammography was reduced more than 60 percent and screening guidelines pertaining to the use of mammography were followed.

Plans: The data base accumulated over the past six-plus years is very large and complex. The only detailed analysis of these data thus far has been by the Beahrs Group and published in 1978. As the project drew to a close, the major objectives were to obtain the best possible use of this data base and to identify its full potential as well as its limitations. Much has been done since the Beahrs Group's work and much remains to be done. To that end, we have established a new Ad Hoc working group known as the Data Management and Advisory Group (DMAG) with representation from the National Cancer Institute staff, Screening Project Directors, and the American Cancer Society. This group is proposed to oversee and provide guidance for the NCI to perform appropriate analyses. The first step is underway to prepare a comprehensive descriptive paper which will characterize the entire data base and to outline an organized means to allow access to it. The full group has met twice, subcommittees for specific tasks have met, and a tentative schedule for a first rough draft of the descriptive paper has been set for midsummer and the final manuscript by the fall.

Publications:

Bland, K.I., Buchanan, J.B., Gray, L.A., Hagan, T. and Weisberg, B.: The effects of exogenous estrogen replacement therapy on the breast: breast cancer risk and mammography parenchymal patterns. Cancer March 1980.

Bland, K.I., Buchanan, J.B., Kuhns, J.G., Moore, C. and Polk, H.C., Jr.: Results of breast cancer screening in women less than 50 years of age. JAMA 1980.

Carlile, T: Breast cancer detection. Cancer 47 No. 5, March 1, 1981.

Gohagon, J.K., Rodes, N.D., Blackwell, C.W., Darby, W.P., Farrell, C., Herder, T., Pearson, D.K., Spitznagel, E.L., and Wallace, M.D.: Individual and combined effectiveness of palpation, thermography, and mammography in breast cancer screening. Preventive Medicine 9: 713-721, 1980.

Isard, H.J.: Thermography and breast cancer detection. Acta Thermographica.

Letton, A. H. and Mason, E. M.: Treatment of nonpapable carcinoma of the breast. Cancer 46, No. 4, 1980.

Letton, A. H. and Mason, E. M.: Five-year plus survival of breast screenees. American College of Surgeons, (In Press)

Milbrath, J.R., Bauermeister, D., and Moskowitz, M.: Breast cancer screening. CRC Press.

Mittra, N.K., Verner, E.W., and Rush, B.F., Jr.: A comparative study of breast cancer in the black and white population of two inner-city hospitals. J. Surg. Oncol. 15: 11, 1980

Pearson, D. K., Blackwell, C. W., Sullivan, W. K. and Rodes, N. D.: Breast cancer screening, a six-year experience. Missouri Medicine, pp. 713-715, December 1980.

Slotman, G.J., Milazzo, J., Jain, K.M., Swaminathan, A.P. and Rush, B.F., Jr.: The effect of radiofrequency hyperthermia on the Ca755 murine adenocarcinoma. Cancer 46: 1992, 1980.

Contract 45092: Study of the Natural History of Genital Tract Anomalies and Cancer in Offspring Exposed In Utero to Synthetic Estrogens

From 06/24/74 to 06/23/82

FY 81: 0 (Ann. \$200,333)

Dr. Raymond H. Kaufman, Baylor College of Medicine, Houston, Texas 77030

Objectives: The aim of the DESAD (DES-Adenosis) Project is to access comprehensively the magnitude and severity of the health hazards to DES-exposed female offspring which may have resulted from the administration of exogenous, synthetic estrogens to their mothers. Prevalence and incidence rates of epithelial changes and gross anatomical changes will be determined. The risk and incidence of cancer and pre-cancerous conditions will be observed and studied. A primary objective is to report on results that will assist others in identifying, locating, examining and treating DES-exposed offspring, if recommended as a result of this study.

Accomplishments: Baylor has enrolled 1,346 participants, 190 of which are controls. We have seen approximately 1,000 participants this year, the majority for their follow-up examinations. This year two cases of clear cell adenocarcinoma of the vagina were found during routine yearly exams on two of our participants. Both cases were detected early before the cancer had time to spread and were successfully treated by their private physicians who worked in close association with us. At this time, the prognosis for these patients appears excellent. The ages of both participants were above what is generally considered the age of highest risk for DES exposed females to develop clear cell adenocarcinoma. Both participants have been followed for a number of years in the DESAD Project and neither had shown previous signs of any dysplastic changes before the invasive carcinomas were found.

Our exposed and control participants maintain a high interest in our program through continued physical examinations and psychological support. To keep the participants up-to-date on the project's latest findings, a pamphlet was put together by all the DESAD Centers and distributed to the participants. The pamphlet has been well received. We feel that this is a positive step in keeping our participants interested and participating in the Project. The DESAD Project is still closely following pregnancy outcome in DES exposed women. We are finding that a significant number of women exposed to DES in utero have unfavorable pregnancy outcomes (spontaneous abortion, premature delivery, ectopic pregnancy). We feel that this finding is an important contribution, although it was not a part of the original DES study. A major contribution of DESAD investigators and staff continues to be that of professional and public education. It is now being shown that many of the risks at pregnancy are manageable if both the DES exposed woman and her obstetrician are aware of the necessity of more frequent office visits and more frequent vaginal examinations.

Project Officer: Robert T. Bowser, Ph.D.

Plans: Diagnosis of two clear cell adenocarcinomas of the vagina does not significantly raise the statistical risk of cancer to DES exposed women. It does however, emphasize the importance of long-term study of DES exposure. Our investigators and staff feel this study should be on-going since there are many questions that only time can provide answers.

Publications:

Kaufman, R. H., Adam, E., Binder, G. L., et al; Upper Genital Tract Changes and Pregnancy Outcome In Offspring Exposed In Utero to Diethylstilbestrol. American Journal of Obstetrics and Gynecology. Vol. 137, No. 3, pp. 299-306, June 1, 1980.

Kaufman, R. H., Adam, E., Grey, M. P., et al; Urinary Tract Changes Associated With In Utero Exposure to Diethylstilbestrol. Obstetrics and Gynecology. Vol. 56, No. 3, pp. 330-332, September 1980.

From 06/28/74 to 06/27/82

FY 81: 0 (Ann. \$210,333)

Dr. D. Townsend, University of Southern California Medical School, 1414 South Hope Street, Los Angeles, California 90015

Objectives: The aim of the DESAD Project is to assess, comprehensively, the magnitude and severity of the health hazards to DES-exposed female offspring (specifically, incidence of adenocarcinoma) which may have resulted from intrauterine exposure to synthetic estrogens. Vaginal and cervical tissue changes will also be assessed and studied.

Accomplishments: Identification of those patients who have been exposed to DES as well as a number of control patients, (those who were not exposed to DES) have long since been identified and contacted. Follow-up examinations to these patients for the last six years have enabled the DESAD project to make some recommendations for their care. Those have been expressed in several papers published by the DESAD project as a whole, i.e., the paper on vaginal epithelial changes, pregnancy paper, etc. The second newsletter written through a collaborative effort of the centers will soon be circulated to advise the DESAD participants involved in the project of the latest information and findings regarding DES. New standardized forms to record socioeconomic status data and pregnancy outcomes have been developed and are currently being used. The pregnancy form is anticipated to provide more information regarding pregnancy wastage in DES-exposed and non-exposed participants.

Plans: Participants will continue to be examined and interviewed through June, 1982. The above mentioned study to determine risk factors and incidence rates of vaginal epithelial changes will continue and it is expected that all of the specific aims of the project listed in the protocol will be accomplished. Plans are currently underway to seek five additional years of funding from NIH as the DESAD investigators feel that long-term follow-up is necessary to assess the risk of cancer in DES-exposed women.

Project Officer: Robert T. Bowser, Ph.D.

Contract 45124: Study of the Incidence and Natural History of Genital Tract Anomalies and Cancer in Offspring Exposed In Utero to Synthetic Estrogens

From 06/01/74 to 06/30/82 FY 81: 0 (Ann. \$456,667)
Dr. Leonard T. Kurland, Mayo Foundation, Rochester, Minnesota 55901

Objectives: The aim of the DESAD (DES-Adenosis) Project is to assess, comprehensively, the magnitude and severity of the health hazards to women exposed in utero to exogenous synthetic estrogens (primarily non-steroidal). Prevalence and incidence rates of vaginal and cervical epithelial changes and other abnormalities in the lower reproductive tract will be estimated for the general population of exposed females. In the course of follow-up, frequencies of dysplasia, squamous carcinoma, and adenocarcinoma will be determined. The risk of above mentioned abnormalities in DES-exposed females will be compared to an unexposed cohort. The natural history of vaginal and cervical epithelial changes will be studied. The effectiveness of certain procedures (cytology, histology, colposcopy, palpation, etc.) in the screening of DES-exposed offspring will be evaluated.

Accomplishments: The Mayo Local Center continues to enroll, examine, and follow DES-exposed offspring and a comparison group of unexposed women. As of April 1, 1981, 1,012 participants were enrolled. Examinations (gynecologic exam including colposcopy, Pap smears, iodine staining, and biopsies if indicated) and general health history interviews are done on a yearly basis for all of these women and recorded on standardized forms. By September 1, 1981, more than half of these women will be seen for their fifth or sixth yearly examination and interview. There is a continued emphasis on maintaining close contact and a high level of interest among the participants. An information leaflet describing the Project and its accomplishments was distributed to the participants in January of 1981.

The Mayo Foundation also serves as the National Coordinating Center for the DESAD Project. Data from the four local centers continues to be received, edited, and analyzed. Project-wide protocol, procedures (quality control of data, development of forms, etc.), and statistical analyses are initiated and disseminated from the Coordinating Center. Over 5,300 participants' files (approximately 330,000 computer cards) are maintained and available for analysis. Analyses are continuing in the following areas: cytologic findings, vaginal and cervical structural anomalies; changes in vaginal epithelial findings over time; comparison of colposcopic, pathologic, and cytologic findings; epidemiology of dysplasia; and a study of exposed twins. Other areas of analysis include quality control procedures; evaluation of participant recall versus medical records information, selection bias, and pregnancy outcome in DES-exposed offspring.

Project Officer: Robert T. Bowser, Ph.D.

Plans: Participants will continue to be examined and interviewed through June, 1982. The above mentioned analyses will continue and it is expected that all specific aims of the Project listed in the Protocol will be accomplished. Plans are currently underway to seek five additional years of funding from NIH as the DESAD investigators feel that long term follow-up is necessary to assess the risk of cancer in DES-exposed women.

Publications:

Rabboy, S.J., Szyfelbein, W.M., Goellner, J.R., Kaufman, R.H., Taft, P.D., Richart, R.M., Gaffey, T.A., Prat, J., Virata, R.L., Hatab, P.H., McGorray, S.P., Noller, K.L., Townsend, D.E., Labarthe, D.R., Barnes, A.B.: Dysplasia and cytologic findings in 4,589 young women enrolled in diethylstilbestrol adenosis (DESAD) project. Am. J. Obstetrics and Gynecology.

Contract 45157: Study of the Incidence and Natural History of Genital Tract Anomalies and Cancer in Offspring Exposed In Utero to Synthetic Estrogens

From 06/27/74 to 06/26/82 FY 81: 0 (Ann. \$727,333)
Dr. A. Barnes and S. Robboy, Massachusetts General Hospital, Boston,
Massachusetts 02114

Objectives: The aim of the DESAD (DES-Adenosis) Project is to assess, comprehensively, the magnitude, severity and natural history of the health hazards to DES-exposed female offspring which may have resulted from the administration of exogenous, synthetic estrogens to their mothers. Prevalence and incidence rates of vaginal epithelial changes and precancerous squamous and glandular lesions will be determined.

Accomplishments: The project's study protocol, developed and implemented by the four cooperating institutions, continues to be followed. As in the past, standardized examinations are conducted yearly for each participant as outlined in the Manual of Procedure.

Contract obligations for the number of subjects enrolled at the MGH Center have been met. As of March 1981, 1,563 participants are enrolled of whom 377 are controls and 272 are DES-exposed identified by prenatal record review. These numbers exceed the contracted minimum numbers.

Gynecologic exams, including cytology smears and biopsies and health history are conducted according to protocol.

The MGH Center has played a major role in analysis of project- wide data and in the preparation of this data for publication. Topics include dysplasia, hysterosalpingographic studies, pregnancy wastage and management of the DES-exposed woman.

Plans: Participants will continue to be examined and interviewed through June, 1982. Plans are currently underway to seek five additional years of funding from NIH as DESAD investigators feel that long term follow-up is necessary to assess the risk of cancer in DES-exposed women.

Project Officer: Robert T. Bowser, Ph.D.

Publications:

Barnes, A.B., Colton, T., Gundersen, J.H., Noller, K.L., Tilley, B.C., Strama, T., Townsend, D.E., Hatab, P., O'Brian, P.C.. Fertility and outcome of pregnancy in women exposed in utero to diethylstilbestrol: preliminary findings from the DESAD Project. New Engl. J. Med., 1980; 302:609-613.

Robboy, S.J., Noller, K.L., Kaufman, R.H., Barnes, A.B., Townsend, D., Gundersen, J.H., Nash, S.. Prenatal diethylstilbestrol (DES-exposure): recommendations of the Diethylstilbestrol Adenosis (DESAD) Project for the identification and management of exposed individuals. 1980, DHEW publication no. 80-2049.

Dickersin, G.R., Welch, W.R., Erlandson, R., Robboy, S.J.. Ultrastructure of 16 cases of clear cell adenocarcinoma of the vagina and cervix in DES exposed young women. Cancer, 1980; 45:1615-1624.

Loughlin, J.E., Robboy, S.J., Morrison, A.S.. Risk factors for cancer of the testis. New Engl. J. Med., 1980; 303:112-113.

Robboy, S.J., Effects of Exposure to diethylstilbestrol (DES) in utero. In: Collected Letters Int'l. Correspond. Soc. Obstet. Gynecol. 1980; 21:48-50.

Barnes, A.B., Effects of exposure to diethylstilbestrol (DES) in utero. In: Collected Letters Int'l. Correspond. Soc. Obstet. Gynecol. 1980; 21:50-52

Contract 55174: Comprehensive Cancer Center Communications Network
Roswell Park Memorial Institute

From 5/1/75 to 11/15/81 FY 81: \$89,888 (estimate)
Dr. Edwin Mirand, Roswell Park Memorial Institute, Department of Health, State
of New York, 666 Elm Street, Buffalo, New York 14263

Objectives: It is recognized that there is a need to provide community practitioners access to the expertise located at the Comprehensive Center. The public also needs to be aware of advances in diagnosis and treatment which represent new hope and which leads to increased individual action towards prevention. There is also a mandate to meet the needs of cancer patients, who more often are desiring information about their disease and its management and who require assistance in coping with its emotional and financial consequences. The Cancer Information Service represents a multi-faceted attempt to respond to these needs by enhancing the availability of cancer-related information throughout New York State.

Accomplishments: Roswell Park operates two toll-free information services. Can-Dial provides tape-recorded information to more than 25,000 callers per year. It plays an important role in the State Health Department's DES Alert. The Cancer Information Service provides detailed responses to specific questions, referral to community agencies, and counseling to 15,000 persons per year. An analysis of characteristics of callers to the CIS telephone service shows that females outnumber males by three-to-one and that half of all calls come from persons under 40. The most frequent topics of calls are requests for referrals, questions on environmental causes of cancer, specific cancer site information and smoking cessation instruction. The most commonly cited cancer sites are breast, thyroid, colon-rectum, lung, and female reproductive organs. A user survey shows 91% of callers saying their most important questions were answered, with respondents citing the attitude of the counselor and the authoritativeness of the information as important positive aspects. CIS also provides a Nurse to Nurse telephone consultation service which allows community nurses to discuss specific problems with the Institute's oncology nursing specialists. Cancer education lectures in schools and community organizations reach 15,000 individuals yearly. The Institute publishes Regional Cancer Report, a quarterly newsletter for physicians and allied health personnel with a circulation of 5,000 and a Cancer Education Newsletter for school teachers and administrators. Circulation is 6,000. CIS also produces informational news releases which receive wide publication in newspapers throughout the State. CIS plays an important role in promotion and scheduling of Roswell Park Memorial Institute's cancer screening clinics.

Plans: Continued promotion, operation and evaluation of the telephone information services are foremost in future planning. Evaluation of cancer screening promotion will be conducted. Enhancement of relations with ACS, the New York State Health Department, and other statewide organizations are important to the continued operation and effectiveness of the CIS.

Project Officer: Thomas Kean

Publications:

Mettlin C., Mirand, E.A., Sciandra, R. and Walsh, D.: Public Use of Cancer Information Service. In Hobbs, P. (Ed): UICC Technical Report Series, Volume 55: Public Education About Cancer. Geneva, International Union Against Cancer, 1980, pp. 93-101.

Mettlin, C., Sciandra, R., Walsh, D. and Mirand, E.A.: Attitudes and Knowledge of Public School Teachers With Regard to Cancer Education to appear in UICC Technical Report Series: Public Education About Cancer.

Mirand, E.A., and Sciandra, R.: Public Role: Summary of Safeguards and Warning Signals. In Murphy, G.P. (Ed): Cancer: Signals and Safeguards. Littleton, Mass., PSG Publishing Company, 1980, pp. 61-66.

Mirand, E.A., and Sciandra, R.: Common Questions About Cancer. In Murphy, G.P. (Ed): Cancer: Signals and Safeguards. Littleton, Mass., PSG Publishing Company, 1980, pp. 209-213.

Contract 55224: Comprehensive Cancer Center Communications Network - Memorial Sloan Kettering Cancer Center

From: 6/30/75 to 11/15/81

FY 81: \$58,000 (estimate)

Dr. Guy F. Robbins, Memorial Sloan Kettering Cancer Center, 1275 York Avenue,
New York, New York 10021

Objectives: The Office of Cancer Communications was established in 1975.

In addition to its goal of making knowledge about cancer more available to the general public and to health professionals, the communications staff is concerned with the development of techniques to motivate these audiences to make greater use of this knowledge. Specific objectives of the communications program are: (1) to provide timely, accurate, useful cancer information; (2) to provide health professionals with information on the detection and management of cancer; (3) to improve methods of referring the public to physicians and other resources; and (4) to increase the interchange among health professionals of up-to-date cancer knowledge.

Accomplishments: Communication strategies to reach Black women with information about breast cancer, breast self-examination, and breast screening have been refined. Based on focus group studies among Black women of central Harlem and also by use of telephone and central location interviews, a promotion plan was developed for the Breast Examination Center of Harlem.

A collaborative study with Cancer Control has been initiated to design and pre-test two survey forms which will: (1) measure physicians' perceptions of cancer among Black New Yorkers and (2) collect baseline data on attitudes, knowledge, and practices related to cancer among Black New Yorkers.

The Cancer Information Service telephone inquiry system continues to be one of the most visible and successful programs of the communications office with approximately 12,000 calls handled annually. Approximately 10 percent of callers are health professionals; over 90 percent of users surveyed as part of the regular CIS evaluation report that they are satisfied with the service; approximately 60 percent of callers report that they took a specific health-related action as a result of using the CIS, approximately 25 percent of callers to the service have used the CIS at least once before; and 96 percent of callers report that they would refer a friend or relative to the CIS.

The communications office participated in the City-Wide Conference on Smoking and Health which was conducted in November 1980.

The staff prepared a breast self-examination curriculum for use in a health center in the south Bronx.

More than 50,000 individual pieces of literature are distributed by the communications office yearly through its Publication Checklists.

Plans: Plans include continuation of all public and professional education projects with emphasis on evaluation and reaching special target audiences. A comprehensive system for physician referral in the New York City area will be developed.

Project Officer: Thomas Kean

Publications:

Adams, Miriam: Value of a Communications Office At a Comprehensive Cancer Center. In Burchenal, M.D., and Oettgen, M.D., (Eds): Cancer Achievements, Challenges, and Prospects for the 1980s. New York, Grune & Stratton, 1981.

Contract 55228: Comprehensive Cancer Center Communications Network
University of Wisconsin

From 6/1/75 to 11/15/81

FY 81: \$71,900

Dr. Robert O. Johnson, Wisconsin Clinical Cancer Center, University of
Wisconsin, 1900 University Avenue, Madison, Wisconsin 53705

Objectives: The Communications Office/CIS serves as a focal point to which the public and health professionals can turn for information, assistance and advice about cancer and cancer-related resources in Wisconsin. The staff is expected to develop non-duplicative materials, resources and approaches necessary to share its information with appropriate audiences and to work with other cancer-concerned agencies.

Accomplishments: Cooperated with ACS on smokers' hotline for Great American Smokeout. We are continuing to experiment with ways to increase call load potential through reorganizing internal staffing and reviewing operational procedures. As a result we handled a record number of inquiries in 1980-81.

Overall respondent satisfaction with WCIS as reported in our 1980 user survey: very satisfied - 79%; satisfied - 18%; dissatisfied - less than one-half of one percent; very dissatisfied - less than one-half of one percent; missing data - 3%. There were 215 respondents.

Respondent self report of actions taken as a result of WCIS call: Passed information on to other persons - 36%; talked with my doctor - 18%; nothing - 13%; made appointment with doctor - 10%; asked doctor about tests - 10%; contacted agency recommended - 9%; used information for research project - 9%; other actions taken - 8%; asked for a second opinion - 7%; started regular self-exams - 7%; reduced environmental exposure - 6%; reduced or quit smoking - 4% (total exceeds 100% because respondents were instructed to indicate all applicable responses).

An in-depth cancer information and CIS awareness campaign aimed at the rural audiences has been developed.

Plans: Continue the rural campaign and evaluate its success. Work with the Committee on Black Americans in Milwaukee. Continue to develop target group cancer information promotions, with evaluation a major component of each proposal.

Publications:

1980 Wisconsin Cancer Information Service Statistical Report, Peters, Hudson A., 1981.

Wisconsin Cancer Information 1980 Nonprofessional Caller Survey Study Report, Roston, Diane M., Blandford, Kathleen K.

Developing an Evaluation Strategy: A Client Research Model; Roston, Diane M.;
Information and Referral: The Journal of the Alliance of Information and Referral Systems, Vol. II, No. 1, Fall 1980.

Project Officer: Thomas Kean

Wisconsin Clinical Cancer Center Patient Education Needs Assessment Report,
October 1980, Nowobielski, Linda L.

Wisconsin Clinical Cancer Center Public Education Program Model Development
Preplanning Report, Wisnefsky, Beth M., December 1980.

Stefansson, Maggie; Cancern - quarterly newsletter sent to 15,100 Wisconsin
health professionals.

Contract 55229: Comprehensive Cancer Center Communications Network
Massachusetts

From 6/30/75 to 11/15/81

FY 81: \$109,000 (estimate)

Dr. W. Bradford Patterson, Sidney Farber Cancer Institute, 44 Binney Street,
Boston, Massachusetts 02115

Objectives: To increase the public's knowledge and awareness of cancer, including general information, prevention, detection, treatment, rehabilitation, and continuing care. Special target groups include employees at the worksite, Blacks, and Spanish-speaking people.

Accomplishments: (1) Cancer Information Service (CIS) toll-free telephone system for four New England states, responding to following number of calls (October 1, 1980 - September 30, 1981): Massachusetts - 6,370 calls; Maine - 2,000 calls; New Hampshire - 575 calls; Vermont - 390 calls. Maine CIS designated by Maine Bureau of Health as the official state resource for DES public information. (2) Smokers' Quitline (Massachusetts) responded to 1,425 calls; official public information resource for statewide secondhand smoke awareness campaign by Department of Public Health. (3) Cancer information activities: weekly and bimonthly columns in 9 Massachusetts and Maine newspapers (c. 780,000); weekly column in Spanish language newspaper in Massachusetts; exhibits at 20 lay and professional meetings in Boston (distributed 10,000 pamphlets). (4) Results of 1980 needs assessment surveys re cancer education programs in Boston-area companies and minority focus cancer/health education in Massachusetts community health centers prepared for publication. Company survey (N = 150/500) found cancer was ranked fourth behind hypertension, diabetes, and weight control in educational priority; breast cancer and smoking cessation programs were of greatest interest. The community health center survey (N = 30/58) found that 77% serve Spanish-speaking people; 67% serve Blacks; 66% serve primarily females. Breast, cervical, colon, testicular, and lung were cancers of greatest priority for present and future programs. (5) Cancer education activities: conducted or provided 5 programs at worksite, 16 in community; piloted breast cancer education module in worksite and health center settings. (6) "Living with Cancer" symposium for clergy conducted. (7) Miscellaneous: posters targeted to Black and Hispanic audiences; pamphlet (in draft) on sexual concerns of cancer patients.

Plans: Continue to conduct programs and develop and test cancer education packages for use in worksite, community, and health center settings to reach target groups; coordinate statewide symposium on minority health education issues in Massachusetts; pamphlet on financial aid to cancer patients in Massachusetts; revision, reprinting of Cancer Screening: When Is It Worthwhile?

Publications:

Brodsky, S.: Secondhand Smoker: Everyone's Concern. Springfield Daily News, Feb. 3, 1981.

Dolan, C.: Legal Rights of Breast Cancer Patients: How Physicians Can Comply with the Patients' Rights Law. Physician East (in press), 1981.

Project Officer: Thomas Kean

- Hall, D.J. and Wood, M.C. (Eds.): Cancer Screening: When Is It Worthwhile? Boston, Sidney Farber Cancer Institute, 1979 (Second Printing, 1980), 44 pp.
- Heller, K.S.: Changing Guidelines for Cancer Detection Exams. Physician East 3: 8-9, 1981.
- Heller, K.S.: Deciding the Value of Diagnostic X-Rays. Physician East 2: 12-13, 1980.
- Pediatric Oncology/Hematology Newsletter. Boston, Sidney Farber Cancer Institute. Fall, 1980 (Vol. II, No. 3), and Winter, Spring, Fall 1981 (Vol. III, Nos. 1-3).

Contract 55230: Comprehensive Cancer Center Communications Network
Howard University

From 10/1/80 to 11/15/81

FY 81: \$61,000 (estimate)

Dr. Jack E. White, Howard University Cancer Center, Washington, D.C. 20060

Objectives: The overall objective of the Cancer Communication contract is the same as that of the Howard University Cancer Center's Outreach Program, which is to reduce cancer mortality and morbidity in the Washington metropolitan area through:

- a. Dissemination of information on primary and secondary cancer prevention to both lay and professional communities.
- b. Continual assessment of cancer incidence and mortality in Washington area residents.
- c. Ongoing development of collaborative cancer control efforts among organizations and institutions in the Washington, D.C. area.

Accomplishments: Between the months of October 1, 1980 and March 31, 1981, 960 calls were received. Based on planned promotional activities, a total of 700 additional calls are expected between April 1 and September 30, 1981.

During this same period, 40 community education programs were conducted, with a total of 800 participants. The demographic composition of these audiences included a majority of black males and females, followed by Hispanic and white females. The average age range was between 21 and 60 years of age. Eighty-five percent of the program participants were from the District of Columbia, with the remainder coming from nearby Maryland and Virginia suburbs.

Other accomplishments included:

- a. The promotion of the cancer curriculum in the D.C. Public School system.
- b. The joint sponsorship of the YWCA ENCORE Program.
- c. The finalization and preliminary implementation of an overall communications strategy which included a minority marketing plan.
- d. The updating and refining of the physician referral service and the CIS consultant list.
- e. The installation and initiation of the Can-Dial system.
- f. The implementation of an evaluation process that facilitates prospective planning and management.
- g. The full integration of the communications program with other cancer control and cancer center activities.

Project Officer: Thomas Kean

Plans:

- a. Expand the service area to include the states of Virginia and West Virginia.
- b. Expansion of CIS hours of operation to 8 p.m. on three nights per week.
- c. Total refinement of overall quality control procedures for CIS responses.
- d. Publication of public and patient education fact sheets.

Publications:

Butler, L., and Theiss, P.: Cancer Information Service Brochure. Howard University Cancer Center, 1981.

Butler, L.: Howard University Cancer Center--Just a Beginning. J. National Medical Association, Vol. 73, No. 1: 67-69, 1981.

Contract 55232: Comprehensive Cancer Center Communications Network - Connecticut

From 6/30/75 to 11/15/81

FY 81: \$68,000 (estimate)

Dr. Jack W. Cole, Yale University, 155 Whitney Avenue, New Haven,
Connecticut 06520

Objectives: The Comprehensive Cancer Center Communications Network serves as a focal point to which the public and health professionals can turn for information, help and advice. It:

- o jointly sponsors the Cancer Information Service (toll-free telephone line) to give cancer information to the lay public and health professionals;
- o originates and runs, in collaboration with other groups and agencies, specific educational and informational programs for health professionals;
- o develops and distributes promotional materials, especially as it relates to target populations; and
- o provides support to organizations which bring together allied health professionals who deal with cancer patients.

Accomplishments: Among the accomplishments since October 1980:

- o The Cancer Information Service began its fifth year of service. Two major promotions (Great American Smokeout in November 1980 and Women's Cancer Awareness Week in March 1981) were aimed at specific audiences. Women's Cancer Awareness Week resulted in activity for the phone service and also programs coordinated locally. Statistical information for this campaign is being processed.
- o The first New England Oncology Nursing Conference was held in October 1980 cosponsored by a number of organizations in Maine, New Hampshire, Massachusetts, Rhode Island, Vermont, and Connecticut. The conference attracted three times as many nurses as the committee's original objective; content evaluation showed the conference was of high calibre.
- o Educational programs for allied health professionals included a Workshop for Mastectomy Fitters and Reach To Recovery Volunteers and a series of ten monthly, day-long conferences for Level II tumor registrars.
- o Three needs assessments are presently being conducted among:
(1) licensed registered nurses in the state to determine the smoking habits; (2) radiation technologists and dosimetrists to determine the need for educational conferences; and (3) licensed nurses to determine the need for educational offerings in oncology.
- o The Communications Office continues to administratively staff two groups for health professionals: the Connecticut Oncology Association (for physicians and nurses) and the Social Work Oncology Group of Connecticut (for social workers).

Project Officer: Thomas Kean

- o A Media/Dialogue was held in April for print media representatives to give updated information on patient related research being conducted in the state.

Plans: Plans for the future include:

- o Updated Great American Smokeout and Cancer Awareness campaigns;
- o Anti-smoking programs for nurses, conferences for radiation technologists and dosimetrists, and oncology conferences for nurses;
- o Symposium on nutrition and cancer sponsored with the Connecticut Dietitian's Association;
- o Updating of the physician's referral list for the Cancer Information Service; and
- o Conference for pharmacists and nurses on using chemotherapeutic drugs.

Publications:

McCaffrey, Margo, Morra, Marion E., Gross, Jody and Moritz, Derry Ann. Dealing With Pain. New Haven, CT: Yale Comprehensive Cancer Center and the American Cancer Society, 1980, 80 pp. (being reprinted by NCI).

Contract 55233: Comprehensive Cancer Center Communications Network
Fred Hutchinson Cancer Research Center

From 6/20/75 to 11/15/81

FY 81: \$62,000 (estimate)

Dr. Gail Hongladarom, Fred Hutchinson Cancer Research Center, 1124 Columbia
Street, Seattle, Washington 98104

Objectives: The Communications Office serves as a resource: (1) to assist the lay public, health professionals and minority audiences with their cancer questions by providing accessible information through activities of the CIS telephone service; (2) to develop and maintain programs to provide appropriate and accurate educational materials and information within the community in the form of publications, special projects and cancer-related continuing education. CIS activities are integrated with the Fred Hutchinson Cancer Research Center and its Cancer Control Program activities to avoid duplication and ensure the delivery of reliable, accurate information and services.

Accomplishments: (1) The Communications Office has maintained the statewide Cancer Information Service, responding to an average of 500 calls per month, some from as far away as Alaska. The feasibility of CIS expansion to other states is being studied, providing the NCI guidelines can be demonstrably met and funding is available from NCI. (2) The Communications Office has continued updating resource and information directories for Washington State in order to better respond to cancer-related queries. (3) The Third Annual Cancer and the Clergy Conference, held 26 February 1981, gave members of the clergy an update on cancer care and addressed the need for pastoral care and counseling of terminally-ill patients and their families. (4) A weekly "Cancer Answers" newspaper column is featured in 12 newspapers across the state. Negotiations with two additional newspapers to carry the column are underway. Questions are developed by a work-study student, written and edited for accuracy by the Communications Officer and submitted weekly in news release form. (5) A six-month trial "Cancer Answers" radio campaign was produced, with PSA's running from September 1980 to February 1981. It was found that the service was too costly to produce, but continuation with minimal production and tape re-utilization will be explored. (6) The Spanish Language Project has developed materials for Hispanic populations in rural Eastern Washington, a region densely populated with Spanish-speaking groups. The project has distributed CIS materials and brochures to these groups, of which many are migrant farm workers, through the DSHS Rural Volunteer Service Network in 20 Eastern Washington counties. (7) THE FRED HUTCHINSON CANCER RESEARCH CENTER REPORT, circulated to 12,000 health professionals, provides a quarterly overview of significant protocol and research results and a cancer-related continuing education calendar. (8) The demand for speakers, brochures and other educational materials for health professionals and the public from the Communications Office has increased.

Plans: Plans include: (1) possible CIS expansion to Northern California and Idaho, (2) continuation of THE FRED HUTCHINSON CANCER RESEARCH CENTER REPORT, (3) resource directory updates, (4) evaluation of the Oncology Self-Learning Facility, (5) production and distribution of a permanent cancer exhibit, and (6) a portable, modular unit for use at health fairs.

Project Officer: Thomas Kean

Publications:

THE FRED HUTCHINSON CANCER RESEARCH CENTER REPORT, quarterly publication circulated to 12,000 health professionals.

Hongladarom, Gail, Cancer Information Service. THE PEO RECORD, February 1981.

Contract 55234: Comprehensive Cancer Center Communications Network
North Carolina

From 6/16/75 to 11/15/81 FY 81: \$63,000 (estimate)
Dr. Diane McGrath, Duke University Medical Center, Durham, North
Carolina 27710

Objectives: The project is designed to meet the cancer information needs of North Carolinians, laypersons and professionals. A toll-free telephone service provides responses to questions about cancer and about resources available throughout the State for families as well as for patients with cancer. Similar services are provided for professionals. Nurses and other allied health professionals also benefit from our newsletter which focuses on cancer-related activities in the state. Another newsletter, for laymen, describes cancer activities and concerns of the Comprehensive Cancer Center. To further respond to identified needs, pamphlets and public information programs are developed and produced.

Accomplishments: Between October 1980 and September 1981, the telephone service will have responded to approximately 8,000 telephone calls. Requests for written information (pamphlets) are numerous. Over 100,000 are anticipated. A newly revised and reformatted publications list should allow users to focus on exactly what their needs are and thereby facilitate their choice of materials. The volume of requests handled indicates our users' need for written information and our ability to respond efficiently to those needs. The telephone service continues to gain recognition as a major source of cancer information and referral data; this fact is reflected in our calls. North Carolina Cancergram, with a circulation of 3,400 nurses and allied health professionals, will have been distributed in three issues. Approximately 4,000 laypersons are on the Cancer '80 - Cancer '81 mailing list; three issues of this publication will also have been distributed during this period. A new lay publication is being developed for September 1981 to report on region-wide cancer news. Two six-week public cancer education programs with a total enrollment of 130 participants will have been held. Topics will cover sites of human cancers, treatment modalities, and psychosocial issues in cancer. The hiring of a coordinator for the communications program will have added to our ability to expand our community education and information programs; to recruit, train, and supervise volunteers for the telephone service; and to renew our continuing education programs for the service.

Plans: Plans for activities beyond September 1981 include expanding our non-telephone community outreach. Using established and new networks of cooperating groups, we hope to meet the cancer information needs of community agencies. On-going program evaluation and improvement, as well as the expansion of publication efforts, are also planned.

Project Officer: Thomas Kean

From 6/14/75 to 11/15/81 FY 81: \$141,000 (estimate)
Dr. Denman Hammond, USC Comprehensive Cancer Center, 1721 Griffin Avenue,
Pinney Hall 209, Los Angeles, California 90031

Objectives: To provide current and accurate information on cancer to the public and to health professionals in southern California. Emphasis is placed on reaching minority and high-risk target populations. Target audiences for the USC/OCC are selected on the basis of five criteria: (1) demonstrated high cancer risk for a group; (2) history of limited access to existing medical/information/education resources by that group; (3) significantly large population; (4) desire for OCC programs as evidenced by the cooperation of community leaders and representatives; and (5) location within the USC Cancer Center service area.

Accomplishments: The Cancer Information Service (CIS) responded to approximately 700 calls per month; recruited and trained two new groups of volunteers, bringing the working total to 30; and established a Spanish CIS. CIS promotion utilized print ads, radio and TV public service announcements, pocket calendars, posters, bookmarks, and celebrity educational announcements. A survey was completed of the requirements of 100 radio and TV public service directors. OCC educational activities included creation of two slide/tape programs--on cancer in men and cancer in general; presentation of at least 15 community education programs a month to audiences of 20 persons or more; production of a four-part radio series on cancer; the redesign and update of brochures for the black audience on colo-rectal, prostate, and uterine cancers; and the creation of a general brochure on cancer for the Vietnamese community. Additional activities included co-sponsorship of two workshops on cancer for agencies representing the Black and Hispanic communities; use of the CIS number to promote Breast Examination Training and Porta-Pap programs (CCC/LA); and the restructuring of the Advisory Council for the Hispanic community.

Evaluation activities included: a survey of callers to the CIS; a volunteer satisfaction survey; surveys of hosts and participants of community education programs; a time-motion study of the activities of the CIS supervisor; and computerization of the CIS call record form.

Plans: Community education efforts will continue to be offered to areas outside the Los Angeles basin; additional brochures and audio-visual programs will be developed as needed; the Spanish CIS will be promoted to all of southern California. Other future programs will be based on the evaluation results of existing programs.

Publications:

Cohn, G. (Ed): University of Southern California Comprehensive Cancer Center Consultant Services Directory (IN PRESS).

Cohn, G., Henderson, B., and Vandenberg, J. (Eds): Cancer in Los Angeles County (IN PRESS).

Project Officer: Thomas Kean

Cohn, G., and Vandenberg, J. (Eds): Cancer Center Report, 1980-1981, Vol. 4, Nos. 3 and 4, 12 pp. each.

Cohn, G., and Vandenberg, J. (Eds): Cancer Center Report, 1981, Vol. 5, Nos. 1 and 2, 12 pp. each.

Cohn, G., and Vandenberg, J.: The University of Southern California Comprehensive Cancer Center: An Introduction, 1980.

Cohn, G., and Vandenberg, J.: The University of Southern California Comprehensive Cancer Center: Medical Oncology Program, 1980.

Mullins, Jr., D.L., and Vandenberg, J.: (Eds): Cancer Com-Line, 1980-1981, Vol. 1, Nos. 3 and 4, 4 pp. each.

Mullins, Jr., D.L., and Vandenberg, J. (Eds): Cancer Com-Line, 1981, Vol. 2, Nos. 1 and 2, 4 pp. each.

Mullins, Jr., D.L. and Taylor, S.K.: Facts on Colon and Rectum Cancer for Blacks, 1980.

Mullins, Jr., D.L., and Taylor, S.K.: Facts on Uterine Cancer for Blacks, 1980.

Mullins, Jr., D.L., and Taylor, S.K.: Facts on Prostate Cancer for Blacks, 1980.

Vandenberg, J.: Cancer Answers Column, published weekly in areas newspapers.

Contract 55237: Comprehensive Cancer Center Communications Network - Fox Chase

From 6/30/78 to 11/15/81

FY 81: \$61,000 (estimate)

Dr. Paul F. Engstrom, The Fox Chase Cancer Center, 2201 Burholme Avenue,
Philadelphia, Pennsylvania 19111

Objectives: The goal of the Fox Chase CIS program is to use cancer communications to provide timely, accurate information to the public and health professionals through a balanced program of broad-based large scale information efforts and pilot research projects for specific target audiences.

Accomplishments:

1. Operated a Cancer Information Service toll-free telephone line for the public, handling 6500 calls and letters during this period. The service area includes Pennsylvania, New Jersey, and Delaware.
2. Conducted a survey of older persons in southern New Jersey to ascertain their knowledge, attitudes and beliefs about cancer. In the process, developed a technique for administering a questionnaire to groups with low reading skills or physical impairment.
3. Published a monthly newsletter, Cancer Calendar, for 3000 health professionals in our service area.
4. Held one-day seminars for Catholic Clergy and high school students on pastoral counseling and cancer research respectively.
5. Distributed over 125,000 pieces of literature to the public, other centers, and health professionals.
6. Produced cancer information sheets on three new topics including colon-rectum cancer, bladder and metastatic disease.
7. Began a special cancer information program for public libraries in our area.

Plans: Continue operating the telephone service with a goal of 10,000 calls a year. Develop educational modules based on data obtained from the older persons project. Expand the survey to include health professionals. Repeat Cancer and Science, high school seminar. Continue publication of Cancer Calendar and development of library projects.

Project Officer: Thomas Kean

Contract 55241: Comprehensive Cancer Center Communications Network - Maryland

From 6/28/75 to 11/15/81

FY 81: \$62,000 (estimate)

Dr. T. Phillip Waalkes, The Johns Hopkins University, 601 North Broadway,
Baltimore, Maryland 21205

Objectives: The Office of Cancer Communications/Cancer Information Service serves as a focal point to which these groups can turn for information, help and advice. The objective of the CIS is to disseminate the most accurate and current information about cancer. In addition to a toll-free telephone inquiry system, CIS participates in the development of materials, resources and approaches necessary to conduct meaningful cancer control program activities.

Accomplishments: The Cancer Information Service has received 5,115 calls from July 1980 - March 1981. Requests made to the CIS have increased nearly 83% from the previous year. Referrals from professional organizations and health professionals, as well as direct inquiries from these two groups, have increased by more than 400% from the previous year.

In addition to the telephone program, the workscope of the contract includes public, professional and patient education. The CIS developed an average of 26 public education (approximately 10,000 attendees) and 6 professional education programs (approximately 800 attendees). The CIS provided indirect support to an additional 15 nurse/physician community education programs (approximately 700 attendees). Two patient education exhibits have been completed to augment CIS developed brochures--"Hair Care for Chemotherapy Patients", and "Your Chemotherapy Medications." In addition, the CIS is cosponsoring NEED (nutrition, education, exercise, discussion), a program to meet the need of women who have had a mastectomy. The CIS is also participating in the development of a Baltimore City cancer education and detection program.

Plans: CIS expects to develop education/information programs concerning high incidence cancer; to develop public education audio tapes on specific cancer sites for high-risk groups, to be made available through the Maryland Tel-Med Library; to cooperate with the City Health Department and other cancer concerned agencies in the implementation of a Baltimore City Cancer Education and Detection Program; as well as increase this past year's activities.

Publications:

Harwood, P., Maylor, K., Cox, D. and Pankey, J.: Your Chemotherapy Medications. Baltimore, JHU Publications, 1981. 34 pages.

Cox, D. and Pankey, J.: Get the Facts, Cancer Information Service descriptive brochure. Baltimore, JHU Publications, 1981.

Wilcox, P., Mann, E. and Pankey, J.: NEED: Nutrition-Education-Exercise-Discussion (program brochure). Baltimore, JHU Publications, 1981.

Project Officer: Thomas Kean

Abeloff, M.D. and Cox, D.: Diagnosis and Treatment of Neoplastic Disorders. Baltimore, JHU Publications, 1981. (Annual Postgraduate Course Brochure).

Ettinger, D.S. and Cox, D.: Oncology Seminar Series (Weekly Multi-Disciplinary Conferences) Baltimore, JHU Publications, 1981. Brochure.

Paper presented:

Wilcox, P.M. and Cox, D. Developing a Patient Education Instrument. Oncology Nursing Society Annual Meeting, Baltimore, Maryland, 1981.

Contract 55242: Comprehensive Cancer Center Communications Network - Minnesota

From 6/15/75 to 11/15/81

FY 81: \$74,000 (estimate)

Dr. Bruce Douglass, 200 First Street, S.W., Rochester, Minnesota 55901

Objectives: Like most other communications network contracts, the objectives of this NCI-funded effort at Mayo are to pursue specified tasks in five areas: (1) general information activities; (2) Cancer Information Service telephone project; (3) public and patient education and information; (4) professional education and information (collaborative responsibility); and (5) evaluation, including reporting.

Accomplishments: Progress continued in several areas of contract effort during this fiscal year. (1) Calls to the Cancer Information Service boosted and maintained at record levels. (2) Evaluation of two month-long surveys of CIS users' satisfaction. (3) Syndication of "Cancer Answers" radio program expanded to North Dakota and South Dakota with pre- and post-syndication telephone surveys conducted in both states to test program's effectiveness. (4) "Cancer Answers" weekly newspaper column added new papers to syndication roster--74 papers in Minnesota and North Dakota with a total paid circulation of 312,522. Efforts underway to syndicate in South Dakota papers. (5) Completion and analysis of cancer education program to rural Minnesota women through Agricultural Extension Service homemaker's club network. (6) One-month users' satisfaction survey conducted for Cancer Patient and Family Resource Library, results analyzed and reported. (7) Routine distribution in literature racks within Mayo and two affiliated hospitals of more than two dozen pamphlets, totalling 15,000 pieces. Six thousand pamphlets distributed at various professional meetings. (8) Assistance to Mayo Clinic in handling cancer-related public, patient, and news media inquiries. (9) Recruitment and training of new volunteers for the CIS.

Plans: Great effort will be made to integrate the activities of Mayo's cancer communications contract with its new Exploratory Grant for Cancer Control (CA-29354). Work will continue in all areas listed under accomplishments.

Publications:

Anderson, E.M., and Lukens, N.T. (co-authors with Kean, T.J., et al); article for American Journal of Rural Health (in press).

Project Officer: Thomas Kean

Contract 55243: Comprehensive Cancer Center Communications Network - Florida

From 10/1/80 to 11/15/81

FY 81: \$103,000 (estimated)

Dr. Peter Mansell, University of Miami, Coral Gables, Florida 33124

Objectives: (1) To provide a Cancer Information Service (CIS) for Florida and Georgia to which the public can turn for accurate, up-to-date information about cancer. (2) To serve as Public Information Office for the Comprehensive Cancer Center for the State of Florida. (3) To provide an Office of Hispanic Programs to reach the Hispanic population of the State of Florida with cancer education. (4) To provide an Office for Nursing Programs in oncology for the continuing education of the nursing personnel in the state.

Accomplishments: (1) The CIS has served approximately 8,015 callers from Florida and Georgia in the past year. An evaluation of the Georgia Smoker's Quitline is underway to measure the effectiveness of this project in reducing the smoking habits of 140 participants. The Cancer Center has approved a plan to implement a physician referral service for Dade County. (2) The Public Information Office provides cancer related information to the media on an ongoing basis: 20 news releases and 44 documented articles in Florida and Georgia during this reporting period. A two-minute program on cancer awareness was distributed to 18 radio stations in Florida. (3) The activities of the Hispanic Program have included professional and public education and cancer screening among high-risk groups. Cooperation with the Cuban Physicians' Association and the Cuban Nurses Association in Exile (1436 members) has resulted in continuing education programs for their members. Furthermore, a pilot screening and education program for the Cuban Clinics (HMO's) has been expanded to include three clinics serving a total of 82,000 clients. (4) A number of community education programs were conducted in cooperation with various community agencies (e.g. Leukemia Society of Palm Beach County). (5) Evaluative research methodologies are being applied to all programs.

Plans: (1) CIS: Form Black and Hispanic Advisory Groups to assist the CIS's efforts to these audiences. (2) Public Information: Assist in the development of a Cancer Center newsletter. (3) Hispanic Program: Evaluate and refine the program. (4) Special Project: Identify and address the cancer information needs of the elderly population in south Florida.

Publications:

Comunicacion Entre Usted, Un Paciente Con Cancer, Y Su Medico, Miami, Florida, Cancer Information Service, 1981

Project Officer: Thomas Kean

Contract 55244: Comprehensive Cancer Center Communications Network - Texas

From 10/1/80 to 11/15/81

FY 81: \$62,000 (estimate)

Mr. Stephen Stuyck, University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, 6723 Bertner Avenue, Houston, Texas 77030

Objectives: The Texas CIS serves as a focal point for current, accurate information and programs on prevention, early detection, treatment and rehabilitation as well as carcinogenic agents, unproven methods, and the spectrum of services needed by the patient and family members. Information is provided to the inquiring public through widely advertised statewide toll-free phone lines and is extended to target audiences (including minority, rural and high-risk groups) through more direct educational channels. The CIS helps provide a positive sense of awareness of cancer and projects a correspondingly positive approach in all media projects.

Accomplishments: The phone service was utilized by approximately 10,000 callers during the fiscal year with 93 percent of respondents to an annual survey reporting receiving clear, concise information that answered their most important questions about cancer. Over 40 percent of those deemed needing to took some positive health action as a result of this contact.

Over 50 cancer education presentations were made to organizations, schools and churches--many to minority groups. Special emphasis was put on exploring means to better reach minority audiences with information on risk reduction, diagnosis, treatment, and assessing health care. About 4,000 Blacks and Hispanics were instructed in self-examination procedures and other early detection information on high-risk cancers.

A year-long church-based cancer awareness program involving 1400 families was piloted in two Houston area churches. Evaluation is in progress.

Two minority committees, the Cancer Awareness for Black Advisory Group (CABAG) and Cancer Awareness for Spanish Speaking Audiences (CASSA), composed of minority leaders from many professions and organizations, helped provide planning and organizational contacts of programs and media coverage.

Fifteen health professionals from M.D. Anderson's staff were trained in five new subject areas to help broaden the scope of the CIS speakers' bureau. The bureau began its first year on a widely advertised basis within the Houston area.

About 70 county extension agents from the Texas A & M University Agricultural Extension Service received training in cancer detection, risk reduction, diagnosis and treatment. A handbook was developed by the CIS staff and Department of Prevention to help motivate and instruct agents on implementing educational programs in their local communities.

Plans: An effort is underway to align more formally with organizations in the minority community that have established programs adaptable to on-going cancer education programming. "Cancer referral counselors" will be trained in many Health Department clinics to better meet patient needs. Training will be conducted again in other regions of Texas for county extension agents.

Project Officer: Thomas Kean

Contract 55245: Comprehensive Cancer Center Communications Network - Illinois

From 6/30/75 to 11/15/81

FY 81: \$104,000 (estimate)

Dr. Jan W. Steiner, 36 S. Wabash Avenue, Suite 700, Chicago, Illinois 60603

Objectives: The objectives of the Cancer Communications Network are to:

(1) establish and maintain links for information transfer between community professionals and research centers; (2) optimize referral patterns of cancer patients into and through the health care system, particularly for those who, because of geographic or social remoteness, have found access difficult; (3) reduce time between critical incidents (e.g. between onset of the disease and its diagnosis). It facilitates rapid transmission of accurate information about: (1) cancer, its prevention, diagnosis, treatment, rehabilitation and continuing care; (2) recent or current cancer research and clinical investigations conducted in Illinois, and; (3) referral resources in Illinois available for professionals, cancer patients and their families.

Accomplishments: During the 1980-81 contract year, it is anticipated that in excess of 5,000 inquiries will be received by the Cancer Information service for an increase of approximately 30% over the 1979-80 contract year. Of these inquiries, approximately 75% will be initiated from the lay public and 25% from professionals. If trends continue among lay callers, it is expected that the largest number of inquiries will be generated from families of patients (40%), followed by patients (23%), general lay inquirers (20%) and others (17%). Among professionals, nurses comprise the largest group of callers (30%) with physicians (23%) second. A mass mailing to all licensed nurses and physicians in the state was conducted in early 1981 in order to reacquaint these groups with the services of the ICC communications program and to increase calls from these professionals in the latter half of the year.

Most lay inquiries to the CIS have been answered through phone calls alone (52%). Thirty-four percent of the lay callers also receive printed material. Physician consultation is requested by 35% of lay callers. Professional calls are serviced by a phone call only in 46% of cases while 49% also receive printed material.

In addition to the increase in telephone inquiries for information, requests to the Communications Office for in-service educational programs have increased dramatically. The promotion to nurses has increased the volume of requests for in-service education speakers four-fold.

Plans: Major plans for the coming year include: (1) expansion of continuing education initiatives in cooperation with the Cancer Control program; (2) exploration of the need for additional professional phone consultation services; (3) implementation of a targeted lay public education program about the CIS and its services; and (4) improved liaison with professional and lay groups.

Project Officer: Thomas Kean

Contract 65173: Phase II - Community Based Cancer Control Program
New Mexico Cancer Control Program

From 06/23/76 - 06/22/81 FY 81: 0 (Ann. \$896,000)
Robert DeFelice, M.P.H., Basic Medical Sciences Building, Room 177,
Albuquerque, New Mexico 87131

Objectives: The program is testing, the State of New Mexico and the Navajo Nation, the hypothesis that the coordinated use of all feasible interventions in dealing with certain selected cancers will have significantly greater impact than a fragmented and/or single intervention approach. The focus is on meeting the assessed needs of the people in the community through activities that span the major categories of effort from screening and detection, through pre-treatment evaluation, treatment, rehabilitation, and continuing care. The cancer sites toward which that program will direct its efforts include cancers of the breast, colon/rectum, cervix/uterus, lung and head and neck including skin.

Accomplishments: NMCCP accomplishments are separated into four major categories as follows: (1) Individuals participating in professional education conferences, workshops, tumor boards, rounds, inservice sessions, and similar activities number 2,040. (2) The number of patients screened in the detection/diagnosis component of the program totals 2,100. (3) Person-contacts through public education workshops, mass medical campaigns, and messages may have reached 46,338. (4) The number of board, committee, and interagency meetings held totals 25. Two major projects which include the Kayenta Cancer Control Program (KCCP) and the New Mexico Health and Environment Department (HED) Program are providing a continuing opportunity to observe and document the development and implementation of three distinct health care delivery system models. The KCCP, which has expanded to include the entire Navajo Nation, illustrates the harmonious integration of ethnic cultural health beliefs and practices with modern medical approaches and practices. Furthermore, the project demonstrates the application of the principle of self determination by the Navajo Indians with respect to their health care. The HED project, utilizing an existing service delivery mechanism of 44 clinics statewide, demonstrates the organization and delivery of cancer control activities and services throughout a rural, sparsely populated, and health resource deficient state. These demonstration models have potential for replicability elsewhere.

Plans: Briefly, plans are for an orderly NMCCP phase-out in Year -05 (06/22/81) under the direction of the NMCCP Advisory Board. Key functions have been transferred to permanent agencies. The Kayenta Project has now become the Dine' Cancer Control Program, supported by the Navajo Tribe and covering the entire reservation. The Skin Cancer Project is ongoing and funded by a private corporation (Johnson and Johnson). The Melanoma Registry is well-established and will be maintained by the Cancer Research and Treatment Center. Cancer professional education will continue through the University of New Mexico School of Medicine with the cooperation of the American Cancer Society. Last, the Health and Environment Department will continue a cancer education and screening program for residents of the state of New Mexico.

Program Director: Margaret E. Holmes, Ph.D.

Contract 65252: Metropolitan Detroit Cancer Control Program

From 06/29/76 to 06/28/81 FY 81: \$239,729 (Ann. \$1,895,455)
Dr. Michael Brennan, 110 East Warren Avenue, Detroit, Michigan 48201

Objectives: The Metropolitan Detroit Cancer Control Program (MDCCP) was organized to conduct a demonstration project to test in a defined community the hypothesis that a coordinated approach to cancer control is more effective and results in better outcomes for cancer patients than a fragmented approach. A major objective has been to improve the utilization of available cancer control knowledge and technology within the Detroit community. Demonstration projects have been implemented in public information, public education, screening and detection, diagnosis and treatment, rehabilitation and continuing care for breast, cervical-uterine, colo-rectal, and head and neck cancers. The MDCCP has brought together all major cancer-related interests to plan, operate, and evaluate a regional system for cancer control work.

Accomplishments: (1) A regional public information and public response base for cancer issues with potential for expansion to CIS status has been established. With several target population projects and media promotion, more than 5,550 calls were received. (2) Small group health education sessions on breast and cervical cancer were presented to more than 22,500 women in identified high risk areas. A system of early cancer detection services that has screened annually over 10,000 clients for breast and cervical cancer and 5,000 clients for head and neck cancer has been in operation. Current detection rates are in excess of general population data indicating suitable targeting upon high risk groups. (3) A system for updating and distributing regularized cancer care management criteria and guidelines to major oncology centers of Metropolitan Detroit has been developed. (4) Third party reimbursable cancer specific patient home care has been extended to all hospital based oncology services in the region. The new home care hospice-like program based on the MDCCP demonstration is now accessible to clients outside the demonstration and is operating in a mode which is financially viable. The MCF and Visting Nurse joint projects have provided care to 1,400 cases per year. (5) With program resources, organized rehabilitation and supportive services to more than 6,000 cancer patients annually have been provided. (6) Evaluation and investigations into useful cancer control strategy have become a regular component of community based cancer programs in Metropolitan Detroit.

Plans: (1) Integration of community advisory structures, the Policy Council, and Operations Advisory Committee into the Comprehensive Cancer Center's program of outreach. This includes new membership and cancer control initiatives with communities beyond our immediate region. (2) Integration of the home care program and screening projects into health care system with local funding support. (3) Development of the Public Response Program in anticipation of expansion to Cancer Center sponsored CIS. (4) Initiation of planning for cancer control program project aimed at prevention and health maintenance for older adults. (5) Expansion of epidemiological and sociomedical research dimensions of cancer control demonstration projects.

Program Director: Margaret E. Holmes, Ph.D.

Publications:

Brennan, M.J., Grossbart, A., and Swanson, G.M.: Mass Screening for Cervical Cancer: Strategies for Reaching High Risk Women in an Urban-Industrialized Setting. In Hafez, E.S.E. and Smith, J. (Ed.): Carcinoma of the Cervix. The Hague, Netherlands, Martinus-Nijhoff, in press.

Ingall, J.R.F.: Cancer Control and Tactics for Its Accomplishments in Detroit and Beyond. In Mettlin, C. and Murphy, G.P. (Ed.): Progress in Cancer Control. New York, Alan R. Liss, Inc., 1981.

McNally, J.C.: Maxillo-Facial Prosthodontics. *Oncol. Nurs. Forum.* 8:39, 1981.

McNally, J.C.: New Breast Prothesis. *Oncol. Nurse. Forum.* 8:40, 1981.

McNally, J.C.: Pain Clinics. *Oncol. Nurs. Forum.* 8:33, Spring 1980.

McNally, J.C.: Stress Management. *Oncol. Nurs. Forum.* 8:32, Spring 1980.

Swanson, G.M.: Reaching High Risk Groups. In Mettlin, C. and Murphy, G.P. (Ed.): Coping with Medical Issues: Living and Dying with Cancer. New York, Elsevier North-Holland, in press.

From 11/12/75 to 08/31/81 FY 81: 0 (Ann. \$510,000)
Dr. Charles R. Smart, American College of Surgeons, 55 East Erie Street,
Chicago, Illinois 60611

Objectives: 1. The overall goal of the Hospital Cancer Program is to decrease the morbidity and mortality of cancer patients. This goal is to be achieved by improving the cancer control efforts in each hospital, in the areas of cancer prevention, early diagnosis, pretreatment evaluation and staging, optimal treatment, rehabilitation, surveillance for and treatment of recurrent and multiple primary cancers, and terminal care.

2. An approved cancer program is to be encouraged in each major hospital. A standing multidisciplinary cancer committee is responsible for hospital-wide cancer conferences, quality of cancer patient care evaluations, and a data base to evaluate process and outcome. Upon request hospitals are voluntarily surveyed against established standards. Each hospital is encouraged to strive for an optimal program to meet their special needs. Consultations are available for those that desire to establish a new or improve an existing hospital cancer program.

3. Regional training workshops are conducted for hospital tumor registrars.

4. National site-specific patterns of care studies are conducted on a voluntary basis for both approved and non-approved hospitals.

5. A recruitment program is carried out under the direction of the Field Liaison Program, with a cancer liaison fellow or associate being appointed in each hospital, to establish and encourage the program.

6. This program is in its 17th year of funding from NCI, the American Cancer Society, and the American College of Surgeons.

Accomplishments: 1. Presently there are 925 Approved Hospital Cancer Programs seeing 500,000 newly diagnosed cancer patients yearly. In the past year 396 surveys, 269 consultations and 65 regional workshops were conducted.

2. A Prostate Cancer Patterns of Care Study was reported in October 1980 involving 659 hospitals (14,262 patients) in the short term study and 414 - hospitals (20,323 patients) in the long term study. A study on the histologic classification of melanoma and another on the long term complications of insitu carcinoma of the cervix are underway.

3. Three efforts to improve the use of hospital cancer registries were carried out: (1) based on an audit of hospital registry files, a computerized comparative survival report for each of 490 hospitals covering 1.2 million cancer cases was distributed; (2) based on the computer tapes of 26 central registries comparative statistical reports were prepared for each of their 624 participating hospitals on approximately 850,000 cancers; (3) A minicomputer software package for hospital cancer registries was developed for free distribution.

Project Officer: Donald N. Buell, M.D.

Contract 65285: Cancer Control Program for Clinical Cooperative Groups
Southwest Oncology Group

From 09/30/76 to 03/31/82 FY 81: 0 (Ann. \$756,000)
Dr. Barth Hoogstraten, University of Kansas Medical Center, 3500 Rainbow
Boulevard, Kansas City, Kansas 66103

Objectives: There are fundamental guidelines for management and specific methods of treatment that are of proven benefit for patients with cancer. Group protocols enumerate these guidelines, and for many patients specify the best known methods of treatment. SWOG, through its membership and administrative structure, regularly conducts protocol studies. If more patients were treated accordingly, more would benefit. Thus, the objectives of this program are to expand the number of community based affiliated hospitals and physicians, involve them in Cancer Control activities, promulgate the use of select Group protocols by qualified community physicians, and provide educational activities, quality control, and support services.

Accomplishments: From 01/01/80 to 12/31/80, 370 patients were entered on studies. The most frequently used protocols by disease category were lung, breast, acute leukemia, multiple myeloma, lymphoma, and G.I. There was a significant increase in patients treated during 1980 in communities with a population of less than 25,000. Since program inception, we found that community physicians, participating in the program longer than 1 1/2 years tend to become more active in patient registration, hold their own Cancer Control activities, start their own pilot programs, and evoke communication between themselves and other physicians interested in treating cancer patients in the area, acting as a "mini center." To date, there have been no important differences in compliance with protocol requirements between patients treated in their communities versus those treated in the Member Institution. The Radiotherapy Quality Control program is cataloging Radiotherapy facilities and reviewing compliance. During 1980, 365 educational activities were sponsored with attendance ranging from 68 physician-nurses attending a seminar to 500 physicians, nurses, teachers, and other health professionals attending a workshop. Nurses held 87 educational activities ranging from educating a community nurse in the proper administration of chemotherapy to sending information to Nursing Directors in hospitals and clinics throughout the state and setting up workshops on drugs, side effects, and their management for the respondents. Instruments for evaluation have been developed resulting in questionnaires for the community physicians and Principal Investigators. The Nursing Subcommittee developed a questionnaire and a nursing profile form to determine the role and educational needs of the oncology nurse as they apply to management of patients on protocol.

Plans: Plans are to solidify the involvement of existing affiliated hospitals and physicians, identify the most productive program participants and enlist their input into program planning, strengthen ties between the Centers and communities, promote entry of eligible patients onto select protocols by qualified community physicians, develop the role of the nurse oncologist in Cancer Control, and evaluate the overall impact of the program.

Project Officer: Harry Handelsman, D.O.

Publications:

Al-Sarraf, M., Costanzi, J.J., Dixon, D.O.: Levamisole and chemotherapy in disseminated melanoma. Accepted in Proceedings of Sixth Chicago Symposium, A National Conference on Tumor Progression, 1981.

Fabian, C., Abdou, N.I., Mansfield, C., LoBuglio, A.: A protocol for combined modality treatment for Stage III and IV Hodgkin's disease. Accepted as chapter in Immunopharmacologic Effects of Radiation Therapy, Raven Press, 1980.

Panettiere, F., Leichman, L., O'Bryan, R., Haas, C., Fletcher, W.: Cis-diamminedichloride Platinum (II), an effective agent in the treatment of epidermoid carcinoma of the esophagus. Cancer Clin Trials 4:29-31, 1981.

Pullen, D.J., Falletta, J.M., Crist, W.M., Vogler, L.B., Dowell, B., Humphrey, G.B., Blackstock, R., van Eys, J., Cooper, M.D., Metzgar, R.L., Meydrech, E.F.: Southwest Oncology Group experience with immunologic phenotyping in acute lymphocytic leukemia of childhood. Accepted for publication in Cancer Research.

Vogler, L.B., Crist, W.M., Sarraf, A.M., Pullen, D.J., Bartolucci, A.A., Falletta, J.M., Dowell, B., Humphrey, G.B., Blackstock, R., van Eys, J., Metzgar, R.S., Cooper, M.D.: An analysis of clinical and laboratory features of acute lymphocytic leukemias with emphasis on 35 children with pre-B leukemia. Accepted for publication in Blood.

From 06/30/76 to 05/31/81 FY 81: 0 (Ann. \$262,000)
Mr. T. Raichel, Blue Cross Associations,, 676 North St. Clair, Chicago,
Illinois 60611

Objectives: The Blue Cross Association, with the assistance of the Blue Cross and Blue Shield Plans in Greater New York and Indiana, has extensively studied feasibility factors in third-party payor support of cancer prevention and screening services. The objective of the project is to develop and demonstrate a medically effective and cost efficient cancer screening program that can be offered as a prepaid benefit. The study's significance is that third-party reimbursement of costs helps reduce financial barriers, thereby encouraging consumers to use these services. Also, it will increase the availability and stability of qualified cancer screening providers. Thus, third party payment can be instrumental in further improving cancer survival rates through the support of prevention and early detection.

Accomplishments: Within the contract's six areas of activity during Phase 2 (1978-81), the following was accomplished during the final year: (1) Marketing assessment survey materials, originally submitted for OMB clearance in February 1980, were revised as requested and resubmitted, but OMB approval was not secured and the materials were not field tested. (2) Both participating Blue Cross/Blue Shield Plans completed their administrative feasibility studies and prepared reports indicating that third-party payors can effectively administer the cancer screening benefit. (3) A health education handbook, consisting of detailed protocols, quality assurance standards, planning guidelines and a bibliography, was developed for use by payors and cancer screening providers in delivering the health education services specified in the benefit design. (4) Two evaluation methodologies were developed. The first outlines the methods and data other third-party payors can use in assessing whether and how they can administer a cancer screening program as a covered benefit. The second methodology evaluates the impact of cancer screening services on a stream of future costs. (5) Quality of care standards and administrative guidelines to be met by cancer screening providers were developed. Three areas were investigated in detail: use of paraprofessionals; quality assurance programs for mammography; and pathology review. (6) Continuing developments in the screening, diagnosis, and treatment of breast, colon, cervical, lung and bladder cancers were monitored to determine if the benefit needed to be modified. It was concluded that no benefit revisions were appropriate at this time. (7) On 12/31/80, the Final Report and a four volume Final Feasibility Study presenting the methods, findings and conclusions in all project areas except marketing, were submitted. With OMB non-approval of marketing assessment materials, the contract expired and the study, marketing strategy, training methods for a third-party sales force, and the final marketing report are represented by the 1978 Marketing Assessment Plan, and the questionnaire and background materials submitted for clearance.

Project Officer: Chauncey G. Bly, M.D., Ph.D.

From 06/30/76 to 06/29/81 FY 81: \$100,000
Dr. W.H. Hartmann, Vanderbilt University School of Medicine, Nashville,
Tennessee 37232

Objectives: The purpose of the Pathology Quality Control System (PQCS) is to provide at least two levels of review of the confidentially coded histologic material received on each BCDDP screenee undergoing an operation on her breast and to confirm and tabulate the pathologic diagnoses of benign or malignant (in situ/invasive) breast lesions reported in the Breast Cancer Detection Demonstration Projects (BCDDP). Any difficult cases which received differences of interpretation (less than one percent on initial review) were then reviewed for final resolution by all five members of the Central Advisory Group, after communications with the individual project and hospital pathologists, to obtain all additional material or information available for review.

Accomplishments: Over 15,500 cases, represented by over 36,000 slides with appropriate reports and data, have been processed through the Pathology Quality Control System and repository, and correlated by the Data Management Center. From 1977-1981, over 2,000 (13.5%) of the over 15,000 cases submitted for review by the Pathology Quality Control System showed cancers, of which a final tabulation and classification of all BCDDP cancers reviewed is being produced. A relatively higher proportion of tumors detected by the BCDDP are small or "minimal" cancers, than in earlier detection programs.

The Principal Investigator (P.I.), Dr. William H. Hartmann, made the following presentation at the September 1979 American Cancer Society Meeting on Breast Cancer: "The Pathology of the ACS/NCI Breast Cancer Detection Demonstration Projects: A Status Report." Although BCDDP screening programs were started in 1973-74, pathology slide and review material began to flow systematically into PQCS only in early 1977.

Plans: The review and classification process will continue on the existing cases in the repository and on any additional cases received up until the expiration date of the contract, June 29 1981.

With proper photomicrographic equipment having been made available, the contractor is building study sets detailing criteria for the diagnoses of all types of breast cancer seen (including in situ) as well as certain atypical or other interesting breast lesions.

A final report to NCI, detailing the experience and problems, will be submitted at the conclusion of the study. The Final Project Pathologists' meeting to review problems and preliminary results was held in Chicago on March 7, 1981.

A grant application by the P.I. has been submitted to maintain the central repository for continued use as part of the BCDDP data bank. Until such proposals for use are funded, NCI will provide for maintenance and accessibility of the repository at Vanderbilt University through at least June 1982.

Project Officer: Chauncey G. Bly, M.D., Ph.D.

Contract 65374: Children's Cancer Study Group

From 09/28/76 to 09/29/81

FY 81: \$322,837

Dr. Denman Hammond, 1721 Griffith Avenue, Los Angeles, California 90031

Objectives: The primary goals of this program are to increase percentage of pediatric cancer patients receiving the best available disease management through a Clinical Cooperative Group Cancer Control Program and to upgrade the skills of physicians in the community. Specific program objectives include expanding the affiliate institution program and the referral networks, providing support services for community physicians, assuring quality control of patient and study data, providing educational programs in pediatric cancer management, evaluating and testing best known treatments in the community setting and promoting rapid dispersal of effective treatment information.

Accomplishments: The Cancer Control Program has provided for the upgrading of the level of medical care through educational programs; planned for and provided the affiliate participants with support staff including nurse-oncology specialists, clinic data managers and consultative physicians and social workers; created a CCP subdivision within the CCSG data center to collect, monitor, analyze and report all CCP related studies; developed and conducted education programs in the referral network of each sponsor institution, held thrice annual meetings for physicians and other health professionals at the parent institutions; and provided to affiliated hospitals updates of best available therapies, major advances in diagnostic or therapeutic procedures, drug toxicities and useful agents, and papers and abstracts reporting significant advances in diagnostic or therapeutic procedures, drug toxicities and useful agents, and papers and abstracts reporting significant advances. During the first 5 years of the CCP, CCSG has enrolled 1,313 patients and recruited 577 physicians at 200 affiliated institutions at the 13 member institutions that are participating in the Cancer Control Program. During the period 10/1/80 - 3/31/81, it is anticipated that we will continue our activities at the same rate, that is, we will enroll about 195 patients from the 213 affiliated institutions, conduct or contribute to 242 educational programs, training programs or seminars, attended by 9,747 registrants.

Plans: The CCSG Cancer Control Committee has developed an impact evaluation plan that will be implemented during the final year of the current funding period. The plan will involve both a physician survey and a chart audit. Concurrently, the patient enrollment and educational activities of the Group will be continued.

Project Officer: Harry Handelsman, D.O.

Contract 65376: Data Management Center for Breast Cancer Detection
Demonstration Project

From 06/30/76 to 06/30/81 FY 81: \$586,340

Dr. G. Foradori, Data Management Center For the Breast Cancer Detection
Demonstration Project, 3624 University City Science Center,
Philadelphia, Pennsylvania 19104

Objectives: In 1973, the Data Management Center (DMC) for the Breast Cancer Detection Demonstration Project (BCDDP) was established by the National Cancer Institute (NCI) to perform all the data collection, conversion, processing and reporting functions for the BCDDP. Its responsibilities included establishment of data collection protocols, development of a manual of operations for data handling and liaison and coordination of the 29 screening centers in the BCDDP. It was further accountable for the proper storage of all screening forms received from the screening centers as to ensure confidentiality, safety and retrieval as necessary.

Accomplishments: For the screening projects active during this year, the data validation and correction process has continued. Verification by the projects of their Long-Term Follow-Up cohorts has been completed. As the screening projects completed the verification of cohorts, the DMC was able to begin retrieval of screenee form sets for keying and computer processing. (Once a screenee was identified as a follow-up cohort member, certain forms previously not keyed had to be processed.) This task should be completed by early June. Corrections received from projects are being applied to the Master file records. As a result of the verification process, 461 new Pathology forms and 1,407 pathology cover sheets were submitted. These are currently being processed for update into the pathology master file. As of April 1981, approximately 4,333 cancers have been reported from 38,314 diagnostic surgeries performed. Staff from the DMC have participated at recent meetings of the recently established Data Management Advisory Group and have also begun to support the work of that group by generating data. In addition, members of that group and the NCI Project Officer met with in March to review the BCDDP Master File and to discuss future use of the data.

Plans: The current performance period for this contract does not cover the time required to complete all tasks, submit all deliverables, and provide continued support for and collection of data. Because of the unique relatedness and interdependence of the data bases for the BCDDP and the Long-Term Follow-Up, a modification to the Follow-Up Data Management and Analysis Center (CN-95444) is being processed to add the screening data center tasks to the statement of work. The modification to CN-95444 will enable the contractor to complete all tasks, submit all deliverables, and provide continued support for collection of data from the ancillary studies and the Data Management Advisory Group recently established to guide appropriate analyses of the large screening data base.

Project Officer: Richard D. Costlow, Ph.D.

Contract 65378: Clinical Oncology Program -- San Jose

From 09/29/76 to 08/31/81 FY 81: 0 (Ann. \$133,000)
Dr. Thomas Barclay, 751 South Bascom Avenue, San Jose, California 95128

Objectives: The main thrust is to unify, coordinate and enhance cancer care within the Santa Clara Valley community. The community approach offers maximal convenience to patients, their families and to referring physicians. It provides for broadening of the scope and application of the latest data from national and regional cancer programs. The community approach also allows greatest utilization of outpatient services; thus the patient can remain in the local setting and reduce inconvenience and cost to the patient. Components necessary for this approach include all aspects of diagnosis, staging, consultation, treatment planning, continuing care & rehabilitation, and data collection & analysis. It is believed that successful implementation of such a program can contribute to more efficient management of cancer patients earlier in their disease process.

Accomplishments: During this contract (9/1/80 - 8/31/81) the program is continuing to operate as originally chartered. No new activities have been undertaken, as specified under our renewal contract; however, all of our established projects such as continuing physician education programs, tumor board rotations, data collection, and oncology nurse coordinators have continued to develop and function independently through each hospital. The various tasks and activities which have operated during this time have focused extensively on data analysis and information retrieval needed to compile a comprehensive final report, as well as giving the needed direction to the individual members of our consortium to continue a functioning cancer program at their respective institutions.

Plans: We anticipate continuation of program operation through the end of August 1981 with indefinite continuation of individual program components at the separate consortium hospitals. For the final year of the program, attention is focusing on extensive data analysis and evaluation as well as on audits of data. We also will be guiding the on-going program activities of this project to make sure they have a solid foundation for continuation.

Project Officer: Donald N. Buell, M.D.

Contract 75215: Implementation of a Community Based Cancer Control Program -
Rhode Island Cancer Control Program

From 06/30/77 to 06/29/82 FY 81: \$398,211 (Ann. \$727,000)
Dr. Fiorindo A. Simeone, RI Department of Health, 75 Davis Street
Providence, Rhode Island 02908

Objectives: This program is testing, in the State of Rhode Island, the hypothesis that, within a defined community, the coordinated use of all feasible interventions in dealing with certain selected cancers will have significantly greater impact than a fragmented and single intervention approach. The focus is on meeting the assessed needs of the people in the community through activities that span the major categories of effort from screening and detection, through pre-treatment evaluation, treatment, rehabilitation, and continuing care.

Accomplishments: In FY 81, a restructured program was developed and implemented. A cancer awareness program, emphasizing prevention, was completed for lung cancer in six inner-city agencies, reaching Blacks, Hispanics, and low-income groups. Educational materials were distributed in Spanish and Portuguese as well as English. Local personnel were identified and trained for continuing the program. Anti-smoking programs have been conducted for school-age children in the public schools. BSE training sessions on a one-to-one basis have been developed for all staff (fifty) in the Providence Health Centers. Model Cancer Clinics have been established for demonstration in four major hospitals. These will continue after the program has ended and are expected to spread to other hospitals. For one of the counties, effective referral patterns for optimal management of the cancer patient are surveyed. Discharge Planning is being strengthened and is assisted by a network of supporting agencies and organizations in the community. A resource manual for distribution to cancer patients is in the process of preparation. A statewide Cancer Rehabilitation Center has been established and is housed at Miriam Hospital. A satellite rehabilitation clinic already has been established in Woonsocket Hospital. Its efforts are primarily directed toward breast cancer and ostomy patients. The Center's three pamphlets on Ostomies have won extraordinarily wide acceptance. A Medical Advisory Board has been appointed for professional matters, including the development of uniform nomenclature and staging. Hospitals are being encouraged to fulfill the criteria for approval by the Cancer Commission of the American College of Surgeons.

Plans: Educational and training programs will be continued in order to leave in the community personnel who can carry on. Model Cancer Clinics will be developed further to become continuing models of excellence. The Medical Advisory Board will continue to plan and encourage professional education in conjunction with other organizations. A coordinated network of agencies will be developed to which Discharge Planning can refer, and which will be included in a statewide Resource Manual.

Project Officer: Veronica L. Conley, Ph.D.

Contract 75347: Clinical Oncology Program - Grand Rapids

From 12/07/76 to 08/31/81

FY 81: 0 (Ann. \$138,000)

Dr. Edward L. Moorhead II, 100 Michigan Avenue, Grand Rapids, Michigan 49503

Objectives: The Grand Rapids Clinical Oncology Program (GRCOP) is a consortium of all five acute care community hospitals in Grand Rapids, Michigan. The major objectives of this program are: (1) to demonstrate that high quality multidisciplinary cancer care can be delivered to the community setting; (2) to demonstrate that the patterns of cancer care can be changed to include new advances in cancer management; (3) to demonstrate that high quality cancer care can be effectively improved through a city-wide, multi-institutional approach which directly involves the practicing physicians in both planning and implementing the program; and (4) to conduct a thorough evaluation of the program and its impact.

Accomplishments: One hundred an eighteen local physicians serving on 14 city-wide cancer site committees have participated directly in writing 45 site specific cancer patient management guidelines. These guidelines have been placed at the nursing stations in each participating hospital. Algorithms (arrow diagrams) summarizing each guideline are attached to the pathology report that goes to the chart of each newly diagnosed cancer patient.

During the past year, the primary focus has been on evaluating the program. A computerized cancer data system has been implemented to assist in analyzing data associated with the GRCOP guidelines. Two preliminary studies have been completed. In both studies patients diagnosed and treated in 1975 (prior to the development of the GRCOP guidelines) were compared with patients diagnosed and treated in 1977 (the first year of program implementation). Of 28 pre-menopausal breast cancer patients with positive axillary nodes treated in 1975, 18% received multidisciplinary consultation according to the criteria established by the GRCOP. This group compares with 85% of the 27 pre-menopausal breast cancer patients treated in 1977. The two-year survival was 71% (1975) versus 81% (1977). In a similar study involving small cell carcinoma of the lung, 26% of the 35 patients diagnosed in 1975 were treated according to the GRCOP guidelines compared with 88% of the 32 patients diagnosed in 1977. The median survival for these groups were 5.5 months and 8.5 months respectively. The 1975 and 1977 patient groups in both studies were similar in terms of age, stage, and ethnic mix. During the remainder of the contract year, evaluations will be completed for key sites of cancer by comparing changes in the pattern of care between the years 1975, 1977, 1978, and 1979.

The city-wide Nursing Committee of the GRCOP has completed and published a site specific set of nursing guidelines for the care of patients with cancer. They have been integrated into the standard care plans in each hospital. In addition, the Nursing Committee has begun a community-wide nursing audit to determine if there have been changes in the pattern of nursing care following the implementation of the guidelines.

Rehabilitation and Continuing Care Coordinators (Masters level graduate students in Medical Social Work) have been placed in participating consortium hospitals.

Project Officer: Donald N. Buell, M.D.

Using problem oriented assessment forms, these specially trained volunteers have identified the rehabilitation and continuing care needs of nearly 300 hospitalized cancer patients. Through the use of a resource manual outlining over 110 agencies and services, each patient has been linked with the appropriate community services to meet their specific needs.

Plans: During the final contract year, a thorough evaluation will be conducted of each major program component. Using the data which has been collected and the computerized evaluation system, the impact of both the development process and implementation of the medical management guidelines will be evaluated. Citywide audits of colon and rectum, breast, and lung cancer nursing care will be completed in order to determine if the patterns of care have changed following the implementation of the nursing guidelines. Finally, the Rehabilitation and Continuing Care Program will be evaluated by measuring impact on the mood and attitude of cancer patients.

Contract 75348: Eastern Cooperative Oncology Group

From 11/26/76 to 4/30/82

FY 81: 0 (Ann. \$1,004,364)

Dr. Marvin Zelen, Eastern Cooperative Oncology Group, 77 Pond Avenue, Brookline, Massachusetts 02146

Objectives: The objectives of the ECOG Cancer Control Program are to accelerate the transfer of current optimum therapy and patient management to community hospitals. This is being accomplished by: (i) community hospital physicians entering patients on ECOG protocols; (ii) the sponsorship of regional and national workshops; (iii) the training of medical personnel in following protocols and in requiring high-quality data on results of treatment. The significance of the Program is that participation has promoted greater investigator interest and activity; improved data collection and established better information delivery systems. Furthermore, community institutions have been able to form their own regional networks of hospitals thereby reaching patients in small, rural or depressed communities. Participation has helped with staff recruitment, assisted in developing oncology seminars and workshops, encouraged multi-disciplinary approaches to patient care and funded attendance at national meetings. These benefits continue to accrue to an ever-widening circle of health practitioners.

Accomplishments: Since the project began, more than 4700 patients have been registered on ECOG protocols. The current accrual rate is 1300/year. At this time, 3 affiliate institutions participate in the Program in conjunction with 21 ECOG member institutions. More than 600 physicians are involved in the Program. To date, 22 regional educational workshops have been supported by the program as well as 14 sponsored symposia at national ECOG meetings. Training workshops have been attended by 484 data managers and nurses at 25 sponsored workshops. Furthermore, data managers and nurse oncologists committees sponsor educational programs at national ECOG meetings as part of the cancer control educational program. The number of IRB's created in response to the ECOG Cancer Control Program is now 96. Presently, 43% of ECOG accrual is from community hospitals.

During 1980, an evaluation plan was put into effect to assess the benefits and accomplishments of community hospitals participating in the ECOG Program. The plan has three components: (i) a detailed and careful analysis of the ECOG data base to compare the population mix of patients, describe noticeable trends with regard to the population of patients registered on studies, determine how well affiliates carry out protocol therapy, compare toxicity rates, etc.; (ii) an extensive survey of affiliates and member institutions to gather data about patients and the influence of participation on non-protocol patients; (iii) case studies of individual community hospitals and networks to capture the uniqueness of the program in selected participants. The survey involves the analysis of more than 3800 forms. Approximately ten institutions will be case studied.

Most noticeable effect of participation revolve around the influence of ECOG on cancer management in community hospitals and the expansion of educational efforts as well as the significant increase in the number of community-based physicians and other health professionals attending national ECOG meetings and participating in ECOG committees and projects.

Project Officer: Harry Handelsman, D.O.

Plans: FUTURE PLANS: The evaluation efforts will be completed and the results circulated. Preliminary results strongly show that cancer patients and their families benefit if modern treatment and patient management can be delivered in suitable institutions close to home. Many patients will forego the opportunity to participate in national studies if travel, unnecessary expense and inconvenience is manifest.

Discussions have begun to plan for continuation of the Program past the funded project period following the holding of an ECOG Cancer Control Retreat during the past year.

Publications:

Becker, Teresa M.: Cancer Chemotherapy, A Manual for Nurses. Boston, Little, Brown and Co. 1981.

Contract 75355: Cancer Control Program for Clinical Cooperative Groups
Radiation Therapy Oncology Group

From 05/02/77 to 05/01/81 FY 81: \$770,000 (Est.) (Ann. \$847,000)
Dr. Simon Kramer, Jefferson Hospital, 925 Chestnut Street, Philadelphia,
Pennsylvania 19107

Objectives: The goal of the RTOG Cancer Control Program continues to be to strengthen the liaison between RTOG institutions and community hospitals in order to increase the number of patients receiving the most up-to-date cancer management. This goal is accomplished through educational programs and through the participation in the activities of the RTOG, including the semi-annual meeting and accession of patients onto protocol and registry studies. The effect of the Cancer Control Program is to transfer the RTOG technology and group discipline from the full-member institutions to their Cancer Control affiliates.

Accomplishments: Beginning May 1, 1981 there will be twenty-three community hospitals functioning as Cancer Control affiliates. Each of these facilities is committed to participating in a number of RTOG registry studies and randomized protocols, and each has surveyed the list of active protocols of the RTOG and has chosen those with which they wish to be involved. A minimum of 10 patients per year must be randomized into the group-wide protocols. In addition, facilities complete the initial registry, soft tissue sarcoma registry and two site-specific registries developed by the Cancer Control Committee.

All facilities are now participating in the RTOG initial registry and since the program began in 1977 approximately 30,000 patients have been entered in this registry from the Cancer Control participants. The colon and larynx registries now contain approximately 1,000 patients and the Cancer Control Committee is undertaking a study comparing aspects of these registries with similar data collected from the full-member RTOG institutions. Participation in the protocol definitive studies has changed from the standard arm process to full randomization. In 1980, 275 patients were randomized onto the RTOG clinical studies by the Cancer Control facilities. As these hospitals continue their participation, the exposure to RTOG protocols should enhance the management of cancer patients because of improved treatment techniques introduced with these protocols.

Plans: Continued participation in registries and randomized studies will be required for all participants, and their submitted data will be monitored for compliance with protocol standards. In addition, an evaluation plan has been designed that will document the impact of the program in the practicing community hospital through a survey of the Patterns of Care in four disease sites. This study is currently underway.

Project Officer: Harry Handelsman, D.O.

Contract 75389: Phase II - A Community Based Cancer Control Program -
Long Island Cancer Council

From 04/13/77 - 03/31/82 FY 81: 0 (Ann. \$862,800)
Mr. Rajeshwar Prasad, 560 Broad Hollow Road, Melville, New York 11747

Objectives: This program is testing, in Nassau and Suffolk counties of Long Island, the hypothesis that the coordinated use of all feasible interventions in dealing with certain selected cancers will have significantly greater impact than a fragmented and/or single intervention approach. The focus has been on meeting the assessed needs of the people in the community through activities that span the major categories of effort from screening and detection, through pre-treatment evaluation, treatment, rehabilitation, and continuing care. Additionally, public and professional education activities were sponsored. Cancer sites selected for this program were breast, cervix/uterus, prostate, and colon/rectum.

Fiscal year 1981 initiated the phase-down portion of the LICC program to take place over the last 18 months of contract performance. Phase out of subcontract activities were initiated with concerted effort toward finding alternative sources of funds to support these activities. Core program activities concentrated on: 1) finding alternative sources of funds for program activities; 2) finalizing data collection and analyses and; 3) preparing the Final Report.

Accomplishments: (1) Education Information: The public information and public education subcontracts were phased out on 09/30/80. During the last six months in operation, the Cancer Telephone and Information Service handled approximately 2,000 calls. Professional education subcontract activities provided: 1) proctosigmoidoscopy courses for physicians, ostomy courses for 150 nurses, a cancer newsletter for professionals, and, in March 1981, a state of the arts conference on "Carcinogenesis of the Major Cancer Sites" with over 200 attendants. Six hospitals were approved for Continuing Medical Education credits. Twenty-seven nurses were registered for courses in oncology nursing. (2) Screening and Detection: All screening and detection subcontracts were phased out on 09/30/80. (3) Treatment: The ambulatory oncology center subcontract was phased out on 12/31/80. This large municipal hospital served 355 patients during its last three months of operation under LICC contract. The majority of these patients were financially disadvantaged. (4) Rehabilitation and Continuing Care: During the last six months of their subcontracts (ending 03/31/81) several agencies funded to provide rehabilitation counseling and psychosocial support to cancer patients and their families will have served approximately 1600 patients and family members. The Hospice program (subcontract ending 12/31/80) served twenty-three patients and their families over a three month period. In addition to patient care, Hospice provided support in the form of patient and family counseling and bereavement groups. There were 74 graduates of training courses for homemaker/home health aides. (5) Data Collection and Evaluation: Twenty-six hospitals continue to submit data on their cancer patients. LICC has completed processing approximately 14,000 tumor registry forms and reports will be sent to community health agencies. A preliminary report which analyzed the data collected in the 1979 Community Cancer Awareness Study was completed. In this report, the knowledge, attitudes and behavior of Long Island residents in regard to cancer is examined in detail. A study examining callers' assessments of the Cancer Telephone and Information Service has been completed.

Program Director: Margaret E. Holmes, Ph.D.

Plans: LICC will vigorously pursue all leads to possible funding to insure the continuation and expansion of the Data Base, which could become a vital planning resource for the Long Island region. The feasibility of a "Consortium of Data Users" is being explored.

All remaining LICC subcontractors will continue to gather and record the data which was part of the requirements of their subcontract. Data collection, processing, and analysis will be emphasized during the last months of the contract; contract activity will be devoted to data analysis and the preparation of the Final Report.

Contract 75391: Implementation of the Hospice Concept

From 9/30/77 to 9/30/81 FY 81: \$20,000 (Estimate) (Annual 653,667)
Dr. Daniel Hadlock and Ms. Fran Dorsky, Riverside Hospital, Boonton Township,
New Jersey 07005

Objectives: The objective of this project is to test the feasibility and effectiveness of the hospice concept in the United States as a viable alternative for the care of the terminal cancer patient at the end stage of his/her disease. Using the St. Christopher's Hospice as a model for the care of the terminal cancer patient, the goals are to: (1) ease the physical discomfort of the terminal cancer patient by employing pharmaceutical and advanced clinical techniques for effective symptom control; (2) ease the psychological discomfort of the terminal cancer patient through programs allowing for active participation in scheduled activities or periods of peaceful withdrawal as determined by the patient; and aid in maintaining the emotional equilibrium of the patient and the family as they go through the traumatic life experience of progressive disease and ultimately the final separation of death.

Accomplishments: Six hundred and eighty patients/families were served during the program support period of the contract (September 30, 1977 - September 29, 1980). After the removal of length of stays that are greatly outside the norm, the average length of stay for time in program is 45.9 days. For the entire program including all patients, the average length of stay has been 68 days. Of all patients in the program, 52% utilize the inpatient facility and stayed on the average 13 days.

The Hospice Program moved from the rented facility to the Riverside Hospital in February 1981 on a temporary basis following the phasedown of governmental funding, September 1980. The administrators are attempting to develop a "hospice consortium" service for a number of hospitals in Morris County. If this is successful, a permanent location for the hospice will be sought. In the meantime, hospice services and staff have been reduced, and the program is currently being supported by Riverside Hospital.

Plans: Collaborative analyses and writing of the final Descriptive Study Report continues with a completion date of September 30, 1981.

Publications:

Lorenz, Lois, "Hospice Volunteer", HOSPICE FORUM, Vol. 1, No. 3, June 1980, Office of Consumer Health Education, College of Medicine and Dentistry of New Jersey, Rutgers Medical School, supported by Grant Number 1T24 MH 15690 NIMH.

Lorenz, Lois, "Hospice: Can We Regulate Caring", HOSPICE FORUM, Vol. 2, No. 1, February 1981, Office of Consumer Health Education, College of Medicine and Dentistry of New Jersey, Rutgers Medical School, supported by Grant Number 1T24 MH 15690 NIMH.

Project Officer: Janet L. Lunceford, R.N., M.S.N.

Baldwin, Marcella and Lorenz, Lois, "Bereavement Manual", May 1981, Office of Consumer Health Education, College of Medicine and Dentistry of New Jersey, Rutgers Medical School, supported by Grant Number 1T24 MH 15690 NIMH.

Contract 75393: Clinical Oncology Program - Indianapolis

From 06/30/77 to 08/31/81

FY 81: 0 (Ann. \$148,000)

Dr. William M. Dugan, 1604 N. Capitol Avenue, Indianapolis, Indiana 46202

Objectives: The Clinical Oncology Program (COP) is a clinical research effort to develop a management program for cancer patients that can be readily implemented within community hospitals. Underlying this innovative program is the hypothesis that sophisticated cancer care can be provided to most cancer patients in a community hospital, thus alleviating the need for patients being routinely referred to specialized centers.

Accomplishments: The implementation phase of the COP ends on August 31, 1981. There were 5,201 site eligible patients admitted to Methodist Hospital; of these, 2,470 (48%) were enrolled in the COP.

The integration of the COP components into the Hospital's Oncology Care system continues as the Department of Nursing has absorbed three COP nurses. The Nurse Administrator for the COP has assumed the position of Nursing Unit Manager of the Hospice Care Unit. The Oncology Unit will be moved to its own floor and a special staff will continue to provide the special personalized care that goes with an oncology unit.

Educational activities involving the COP staff have increased to include 300 programs given since the program began in 1977, and have been attended by 13,500 health professionals and interested individuals.

The Oncology Family Support Group, composed of physicians, nurses and allied health persons, began during the previous year. This support group not only provides educational material, but also brings families together for the mutual sharing of concerns, hopes and frustrations. Guest speakers have discussed the disease cancer, its treatment and psychosocial problems and have included chaplains, social workers, oncology nurses and physicians.

Encouraged by the COP staff, the Indiana State Legislature unanimously passed a resolution to establish a committee to study the feasibility of a community cancer control program throughout the entire state.

Plans: (1) Complete the final evaluation of the project. (2) Continue integration of COP components into the Hospital's Oncology care system. (3) Continue to develop plans for the new Oncology/Hospice Center. (4) Participate in activities of the Indiana State Community Cancer Control Study Committee enacted by the legislature.

Project Officer: Donald N. Buell, M.D.

Contract 75394: Clinical Oncology Program - Allentown

From 06/30/77 to 08/31/81 FY 81: 0 (Ann. \$95,000)
Dr. David Prager, 17th and Chew Streets, Allentown, Pennsylvania 18102

Objectives: The objective of the Clinical Oncology Program is to demonstrate that community hospitals can provide effective multidisciplinary diagnosis, pretreatment evaluation, treatment, rehabilitation and continuing care services to cancer patients in their own community. The Allentown Clinical Oncology Program has met these objectives through the development of diagnosis and treatment guidelines; the formation of an Evaluation Committee; the introduction of the oncology rehabilitation and continuing care team concept strengthening of nursing and allied health professional services for oncology patients and families; and an active program to meet the needs of patients, families, physicians, nurses and allied health professionals in this community.

Accomplishments: A series of management guidelines for the most common cancer diagnoses in the Allentown region, which includes the six cancer sites to be addressed on the National Cancer Institute common evaluation, have been developed, representing over a year of broad based preparation. Guidelines standardizing the staging of 25 cancer sites have been developed and implemented since January 1978, and are updated on a yearly basis.

A multidisciplinary Evaluation Committee functions to gather information to determine whether or not the coordinated approach is being applied to patient care, whether staging is being done, the effect of staging on treatment, the use of rehabilitative and supportive services and how all these considerations affect the quality of patient care in our community. All newly diagnosed patients in the six indexed cancer sites are entered on the Clinical Oncology Program management schemes.

The Clinical Oncology Program and hospital nursing services have broadened the multidisciplinary approach to oncology nursing, resulting in active nurse participation in clinical, educational and administrative policy forming committees, as an approach to oncology nursing care.

Weekly Multidisciplinary Tumor Board and Pelvic Tumor Board Conferences function most prominently as a vehicle for continuing professional education. A significant educational offering is a Core Course in Oncology a 10 week, 64 hour curriculum covering a broad spectrum of topics of interest to nurses specializing in cancer care. The Clinical Oncology Program has sponsored 15 educational seminars in cooperation with various clinical departments and also maintains an active Speakers Bureau.

The Mobile Rehabilitation Team is the core rehabilitation educational and continuing care group for our cancer patients and their families. Emphasis is placed on patient and family preparation for care at home, patient and family counseling and nutritional assessment, education and intervention.

The introduction of the Oncology Mobile Rehabilitation Team has changed the care of cancer patients and their families through coordinated planning of education

Project Officer: Donald N. Buell, M.D.

and direct care during the patient's hospitalization. Additional efforts are directed toward patients being treated in the community through nutritional, educational and community resource programs and towards the continuing care of terminally ill cancer patients through hospice development.

The Allentown COP has an overall outreach objective of providing meaningful support to smaller community hospitals to encourage the growth and development of their cancer programs. The expansion of our outreach activities to include a total of seven programs mandates a strong effort at the strengthening of ties between the practicing physician at multiple institutions and also at the nursing and allied health professional level.

Plans: We plan to direct our current level of effort towards continuation of our existing program activities. Additionally, work will continue in the area of the designated National Cancer Institute evaluation plan, outreach program development, tumor registry computerization, preparation of additional educational seminars and the establishment of a financial plan for the continuation of the Clinical Oncology Program post the National Cancer Institute funding.

Publications:

CANCER FORUM - spring 1980	Surgical Pathology
summer 1980	Nuclear Medicine and Lung Cancer
fall 1980	Cancer of the Prostate
winter 1981	Electron Microscopy

Clinical Oncology Program, Community Resource Manual. Allentown, 123 pp. 1980

Contract 75399: A Community Based Cancer Control Program - Cancer Control
Program of Hawaii

From 08/01/77 to 07/30/82

FY 81: \$1,382,000 Est. (Ann. \$935,400)

Dr. Thomas C. Hall, University of Hawaii, 1236 Lauhala Street
Honolulu, Hawaii 96813

Objectives: To test in the State of Hawaii, the hypothesis that, within a defined community the coordinated use of all feasible interventions in dealing with certain selected cancers will have significantly greater impact than a fragmented and/or single intervention approach. The focus is on meeting the assessed needs of the people in the community through activities that include screening and detection, improved pre-treatment evaluation, treatment, rehabilitation, and continuing care.

Accomplishments: (1) An overall master plan has been developed to implement, monitor and measure the impact of cancer control projects on specific populations, emphasizing the nature, the degrees, and the duration of coordination between interventions and sites. Six different population areas within the state are involved. The system also evaluates cancer control activities in the community not funded by the CCPH. (2) Two comprehensive community surveys have been conducted to assess cancer knowledge and behavior practices related to prevention and detection; significant correlations have been shown for specific sites and practices. These data form the basis for the measurement of the program's progress in the third and fifth years of operation. (3) The Breast Screening Programs on the islands of Kauai and Maui are demonstrations of breast screening and BSE instruction programs in small, rural community hospitals. Community support for the activities has been successfully generated. Efforts to identify and recruit for screening the varied high risk groups on these islands are meeting with success. Over 1,275 women have been screened, interviewed and instructed in Breast Self Examination (BSE). The expected initial increase was observed in the numbers of advanced and early cancers discovered with the advent of the new screening programs. (4) The R/CC model previously developed in Honolulu with Federal funds was transferred to Kaiser, an HMO-type hospital and to Kuakini, a hospital serving a largely Japanese clientele. Over 680 patients and families have been enrolled in these programs and similar programs have been started at the Ob/Gyn/Ped.--Specialty Hospital, Kapiolani Children's Medical Center, as well as at hospitals on the islands of Kauai, Maui and Hawaii. (5) Joint information/education programs were developed with the local American Cancer Society; these contracts are now completed. The first Cancer Information Line (CIL) in the state was established, and a training course designed for CIL volunteers. Over 3,000 calls have been answered since January, 1980. (6) The Hawaii Medical Association is under contract to develop and distribute management outlines for cancers including the five target CCPH cancer sites. (7) Detailed, computerized evaluation systems for on-going and proposed programs have been created. These

Project Officer: Veronica L. Conley, Ph.D.

are designed for multivariate analyses of program variables and comparison of degrees of coordination. This evaluation system also uses CIL information to evaluate impact of CCPH communications on public behavior related to specific cancer control programs. (8) Contracts were let for community hospital oncology programs (CHOP) on the neighbor islands of Kauai and Maui to help them obtain American College of Surgeons' accreditation for their Tumor Programs. (9) The Maui Community College, under a CCPH subcontract, has developed a course for improving cancer nursing skills for senior students and staff nurses. The course features audio-visual teaching aids and self-instructional modules.

Skin/Melanoma prevention and detection programs for the public and health professionals have been added as a fifth site. Cancer Education programs for the elderly have been funded to operate out of community health clinics.

Plans: To: (1) Complete the breast screening, CHOP and R/CC programs on neighbor islands and to compare their impact and the coordination of more than one intervention in specific populations; (2) collect baseline data for comparative purposes in areas not to be served by CCPH programs and from areas with CCPH programs prior to the institution of new programs; (3) produce and distribute management outlines and evaluate impact on practice patterns among physicians; (4) conduct resurvey in Year 05 to evaluate serial change in cancer knowledge and behavior with particular emphasis on geographic comparison of those served and not served by CCPH programs; and (5) plan for completion of the Program--the main focus being: (a) to develop systems for continuation of successful components of CCPH programs in the community, through coverage by third-party payors or by continuation of programs through support of community agencies; and (b) to evaluate quantitatively the impact of this control program on targeted goals.

Publications:

Hall, T.C.: Community Cancer Control in Hawaii. Chapter in "Progress in Cancer Control" Ed. C. Mettlin, N.Y.C., A.R. Liss, Inc. 1981

Murfin, G.D. and Hall, T.C.: Cancer Prevention: Relation of Public Knowledge to Behavior. ASCO Abstract, 1981

Withers, John N. and Wienke, James W.: Hemocult Screening for Colon Cancer by Hawaii's Physicians, Hawaii Medical Journal, Vol. 40, No. 3, pp. 75-78, 1981.

Contract 75400: Phase II - Community Based Cancer Control Program
Community Cancer Control - Los Angeles

From 06/30/77 - 06/29/82

FY 81: \$1,000,783 est (Ann. \$1,122,800)

Dr. Lester Breslow, Dr. Robert McKenna, Dr. Ruth Ann Pick, Dr. Ralph Sachs,
Ms. Helene Brown, 5800 Wilshire Boulevard, Los Angeles, California 90036

Objectives: Community Cancer Control/Los Angeles, (CCC/LA) is a community based cancer control demonstration program, the goal of which is to test the hypothesis that the coordinated use of all feasible cancer control interventions will have a significantly greater impact on the reduction of incidence, morbidity and mortality due to cancer than a fragmented and/or single intervention approach. In order to achieve this goal, CCC/LA has implemented coordinated cancer control activities in the central Los Angeles area for cancers of the breast, lung and cervix. The 17 major programs which CCC/LA conducts are both area-wide and local in scope. Area-wide programs are designed to bring together key persons and organizations in CCC/LA's action area to carry out activities which will affect substantial numbers of health care providers and lay citizens. Local demonstration programs based in the hospital, the school, and the workplace impact on specific geographic areas. Programs centered in the area hospitals focus on early detection of breast and cervical cancer, as well as a coordinated intervention system for patients with cancers of the selected sites. Programs in the primary schools are designed to integrate smoking prevention methods more effectively in academic curricula. Programs centered in the workplace are designed to impact on health behavior including smoking cessation, practice of breast self-examination, and regular acquisition of a pap test.

Accomplishments: (1) Launched a community awareness campaign during October - December 1980, promoting the BET and Cervical programs on 64 Los Angeles area radio stations. Developed posters for various community areas depicting a supportive network of women leaders with the slogan, "Take Control. It's Your Body. It's Your Life". (2) Launched a media blitz campaign in March, 1981 with all of the television stations in Los Angeles. The staffs of the networks received educational presentations from the BET and CCET programs and breast self-examination training was provided to women who desired it. The networks provided public service announcements and features on CCC/LA activities. (3) Conducted a marketing skills workshop to the BET and CCET staffs to enhance their outreach recruitment effectiveness. (4) Launched a business and industry campaign to expand the BET and CCET programs to employed women. (5) Conducted two forums to enhance awareness about cancer and available cancer-related programs to professionals and influential people in the black and hispanic community. (6) Planned and developed a breast cancer seminar for presentation in May, 1981. (7) Conducted a seminar in conjunction with Oncology Social Workers and the California Nurses Association on the psychosocial issues of cervical cancer facing the patient and the family. Seventy people attended, predominantly from the nursing and social work disciplines. (8) Continued co-sponsorship with USC Cancer Center of the ongoing "Cancer and the Clergy" program. Eighty clergy attended the January workshop, serving to broaden the clergy's awareness of cancer and its role in the cancer management team. (9) Nine nurses attended a breast examination training course at the UCLA School of Nursing. This training program insures sufficient training for new BET staff and relief nurses.

Program Director: Margaret E. Holmes, Ph.D.

(10) Six nurses attended a workshop on pelvic examination at UCLA School of Nursing. This workshop augments skills of the 3-B and Porta-Pap CCET nurses and trains relief nurses. (11) The Evaluation Department continued to collect data for the evaluation of the CCC/LA program. Special attention during the last six months has been devoted to BET center patient follow-up, the VNA chart audit, the Los Angeles City Schools and the BET and CCET projects. (12) The two Cervical Cancer Education and Testing programs educated 3,655 women and screened 3,306 women. (13) The five BET Centers trained 9,675 women. (14) The Los Angeles City Schools continues to present effective anti-smoking material through the use of high school peer-instructors. (15) Stop smoking workshops continue for firefighters, retired firefighters, retired police, paramedics and family members. A poster has been produced to promote the workshops and ensure longevity of the program. (16) Efforts continue to seek alternative sources of funds and to establish self-sufficiency for CCC/LA's successful programs after the expiration of the CCC/LA-NCI contract.

Plans: The program will continue with an emphasis on developing mechanisms to more fully implement each activity. Activities to begin program phase-out and the preparation of the Final Report is underway.

Interagency Agreement 80604: Work Hazard Information and
Education Program on Occupational Cancer

From 09/01/78 to 05/31/82

FY 81: \$4,500,000

Mrs. Clinton Wright, Director, Directorate of Training, Education,
Consultation and Federal Agency Programs, OSHA, Department of Labor,
Room N-3476, 200 Constitution Avenue, Washington, DC 20210

Objectives: (1) To support those New Directions Grants or parts of grants awarded by OSHA which relate to occupational cancer. (2) To support an Asbestos Alert Program for current workers exposed to asbestos and their families. (3) To support the development of audiovisual materials on the removal or containment of asbestos in schools and other buildings. These are to be used for the education of state and local departments of health and education, local school boards, architects, contractors and their employees regarding the measures required for protection of workers against asbestos exposures during such procedures. (4) To support workshops or conferences on industry-labor cooperation in the prevention of carcinogenic exposures. (5) Development by NCI and OSHA of an intensive training course on carcinogens in the workplace to be offered at the OSHA Training Institute for OSHA compliance personnel and other appropriate groups. The course materials are to be made available to other educational institutions, New Directions Grantees, labor organizations and industry.

Accomplishments: This is the second IA with OSHA which has been negotiated by the DCCR/DRCCA, NCI. The first, initiated in 1975, was an effort to increase the awareness of workers regarding occupational cancer hazards through the establishment of a cancer information and alert program and the development of educational materials for several categories of workers at high risk for cancer because of occupational exposure to carcinogens. Workers receiving special attention were those in the metal smelting, coke oven, rubber, asbestos and petroleum industries.

The current IA was negotiated in 1978, in the amount of \$700,000, to provide NCI support for that part of the New Directions Grants Program which was related to occupational cancer. Since OSHA has developed effective channels for cooperation with labor groups, it has seemed more appropriate for NCI to pursue its goals in prevention, detection and treatment of occupational cancer for labor groups in close cooperation with OSHA than to try to develop separate contracts and programs. The New Directions grants were made to unions, other labor and trade groups, academic institutions and foundations interested in providing educational programs about occupational safety and health hazards to workers. The grants are normally funded for one year for planning, and one to five years thereafter for development of program. Funding levels will diminish in the latter part of the program with the understanding that the grantees will assume responsibility for continuation when federal support ends. DCCR, NCI, agreed to support those grants or parts of grants which were concerned with occupational cancers.

Project Officer: Margaret H. Sloan, M.D.

In FY '79 the IA was enlarged to include: (1) an increase in support to the cancer-related parts of the New Directions Grants to \$2,285,000; (2) a subcontract for \$715,000 to support a public media program on asbestos to be targeted to current workers and their families; and (3) a special contract for \$500,000 with the Division of Buildings of the New York City Board of Education to develop audiovisual materials for state and local departments of health and education, architects, contractors and their employees regarding the procedures required for safe removal or containment of deteriorated asbestos in schools. These methods would be equally applicable to other buildings in which sprayed asbestos was used between 1946 and 1974 when these also begin to show evidence of asbestos deterioration. These educational materials are being reproduced for distribution through EPA regional offices.

Funds were provided for eight New Directions planning grants concerned with cancer risks in 1978; 44 renewals in September 1979; 16 new grants in August 1980; and fifty renewal applications were reviewed and approved for third-year funding in September 1980.

Plans: In May 1981 the IA was extended for \$4.5 million and modified to (1) continue support for the cancer-related parts of the New Directions grants; (2) develop an intensive training course on carcinogens in the workplace to be offered at the OSHA Training Institute for OSHA compliance personnel and other appropriate groups. (The course materials are to be made available to other educational institutions, New Directions Grantees, labor organizations and industry.); and (3) support workshops or conferences on industry-labor cooperation in the prevention of carcinogenic exposure and other appropriate subjects.

Support of New Directions grants is expected to decrease as more grantees reach the end of their committed support.

Interagency Agreement 80607: Development of Radiographic Teaching Materials
for Physicians on Asbestos Related Disease

From 07/07/78 to 06/15/81

FY 81: 0 (Ann. \$76,231)

Dr. J. Merchant, National Institute of Occupational Safety and Health, 944
Chestnut Ridge Road, Morgantown, West Virginia 26505

Objectives: This Interagency Agreement supports the preparation of a teaching module with an emphasis on the roentgenographic manifestations of asbestos related disease. This agreement will be part of an ongoing contract between the American College of Radiology and the National Institute of Occupational Safety and Health which has produced teaching materials for the Coal Miners' Black Lung Program. This module on asbestos related lung disease will help achieve one of the primary goals of the Division of Resources, Centers, and Community Activities, National Cancer Institute; i.e., the assistance of health professionals in the application of new and available knowledge and technologies to improve the diagnosis and treatment of cancer.

Accomplishments: The module, which is nearing completion, consists of a syllabus, slides and full size chest x-ray reproductions. Associated tables, photographs and case descriptions demonstrate asbestos related disease and simulating conditions. The International Labor Organizations' classification system is described and a sample classification is completed for each film in the set.

Plans: The completed module will be distributed to medical school teaching centers. Mechanisms for the publication of the syllabus are being explored.

Project Officer: Dorothy R. Brodie, M.D.

Contract 85335: Cancer Control for Clinical Cooperative Groups
National Surgical Adjuvant Breast Project

From 05/01/78 to 04/30/81 FY 81: \$215,859
Dr. Bernard Fisher, University of Pittsburgh, 914 Scaife Hall,
Pittsburgh, Pennsylvania 15260

Objectives: The purpose of this program is to increase the number of patients receiving the most up-to-date cancer management. The mechanism used for accomplishing this objective is to introduce clinical trial protocol management in the community setting while maintaining NSABP's commitment to total patient care. Tantamount to the objective of patient accrual are the improvement of skills of community physicians and other health professionals through continuing education, the maintenance of high standards of patient care by providing support service and by instituting quality controls, the dissemination of information about the efficacy of treatments and the ultimate evaluation of treatment in the community setting.

Accomplishments:

1. Patient Accrual: During 1980, 375 cancer control patients from 28 networks were entered on NSABP protocols; the total number grew by 102% in 1980.
2. Benefits to Non-NSABP Patients: The Network Principal Investigators reported that estrogen/progesterone receptor site analyses and pathologic staging are now routinely done on non-protocol patients, and bone scan and liver scan staging and carcinoembryonic antigen analyses are frequently performed.
3. Community Participation:
 - a. Physicians: During 1980, 147 community physicians became involved in the care of NSABP patients. The total number of community physicians grew by 71% in 1980. Network Principal Investigators reported that the routine use of ER/PR analyses increased from 13% to 78% and adequate follow-up of patients increased from 14% to 65% over the course of the network contract.
 - b. Hospitals: Over the course of the network contract accrual increased 227% from community hospitals that were designated as recipients of network activities, and increased only 25% from hospitals that were unaffiliated with the activities supported by the contract.
4. Support Services: The networks have had a monthly average of 380 satellite visits or nucleus consultations to discuss patient management or data management on NSABP protocols.
5. Quality Control: Form delinquency for patients of community physicians is no greater than that of all NSABP patients.
6. Continuing Education: Almost 15,000 people attended 605 educational programs held during the last five months of 1980. Fifty-eight percent of all programs were conducted at sites other than the nucleus. The NSABP and its trials were the primary topics in 148 of these programs.

Project Officer: Harry Handelsman, D.O.

7. Dissemination of Information: Since 1978, network funding has been used to send 241 community physicians to NSABP group meetings. Of those who were not participating at the time of their attendance, 85% are now involved in the care of NSABP patients.

Plans:

1. Continue to meet the objectives of the Cancer Control Network.
2. Develop improved methods of institutional evaluation.
3. Recruit an Educational Coordinator to assist networks in offering support services and overcoming problems of program development.
4. Coordinate and develop studies in the area of the psychosocial aspects of breast and colorectal patient care.

Contract 85375: Implementation of the Hospice Concept

From 6/1/77 to 9/30/81

FY 81: 0 (Annual \$348,500)

Dr. T. Hart Baker, 1956 Webster Street, Room 310, Oakland, California 94612

Objectives: The purpose of this project is to test the feasibility and effectiveness of the hospice concept as a viable alternative for the care of terminally ill cancer patients. This is a collaborative study with two other hospices across the country. To help achieve the major goal of the project a demonstration hospice program, including both inpatient and home care, was developed within the Kaiser-Permanente Medical Care Program, Southern California Region. Results from this in-depth study of three hospice programs will provide valuable and needed information related to the following: patient pain and other physical and psycho-social symptom control; family physical and psycho-social symptom control including a period of bereavement; program utilization; an assessment of staff; and an assessment of hospice care costs.

Accomplishments:

HOSPICE DEMONSTRATION PROGRAM. The Kaiser-Permanente Hospice is an integrated program providing home care, inpatient and day care services, as well as bereavement care. The Program served an average of 63 patients per month.

HOSPICE EVALUATION. All studies have been completed as follows:

1. Patient/Family Study: (October 3, 1979 - September 30, 1980). Writing, editing and coordination of the Final Report is being carried out by the Kaiser-Permanente Evaluation Team.
2. Program Utilization: (October 3, 1979 - September 30, 1980). Utilization Data has been collected on all patients and families served.
3. Staff Assessment: In January 1980, a questionnaire was administered to all staff and volunteers. Information on staff turnover is collected on an ongoing basis. This separate study will be included in the Final Report.
4. Collaborative Cost Analysis: (November 1979 - December 1980). As per agreement with the NCI, the Kaiser-Permanente Evaluation Team implemented a cost variance study of the three participating hospices. This report has been submitted to the National Cancer Institute.

HOSPICE PROGRAM. The Kaiser-Permanente Hospice Program, Southern California Region, will continue providing services after phasedown of NCI program support (October 4, 1980).

Plans: Collaborative analyses and writing of the final Descriptive Study report continues with a completion date of September 30, 1981.

Project Officer: Janet L. Lunceford, R.N., M.S.N.

Contract 85392: Implementation of the Hospice Concept

From 6/1/77 to 9/30/81

FY 81: 0 (Annual \$289,000)

Mr. John A. Hackley, 1015 Center Street, Tacoma, Washington 98411

Objectives: Implement comprehensive program of hospice care providing services for terminal cancer patients and their families through a free-standing inpatient facility, a 24 hour per day/seven day per week home care program, and an integrated bereavement program. Secondly, design and conduct an evaluative study to provide documentation of the development, utilization and services of a hospice program.

Accomplishments: Eight hundred and forty-two patients were admitted to the hospice during the program implementation period of the contract. One third of all referrals came from community physicians. Other major sources were community social workers and discharge planners (39%), and from families (16%). The greatest number of admissions were those with a primary cancer site in the digestive organs (30%), followed by lung cancer (24%) and those of the genito-urinary systems (18%). These three groupings comprised 72% of all primary diagnoses. Slightly more females (52%) than males (48%) were admitted with nearly four-fifths of all admissions over the age of 60 (79%). The hospice served 47% of all Pima County cancer deaths in 1980.

The hospice moved into St. Mary's Hospital in January 1981 following the phase-down of governmental support. The Home-Care component of the program continued unabated. A renovated ten-bed inpatient hospice unit within the hospital opened in May 1981.

Plans: Collaborative analyses and writing of the final Descriptive Study report continues with a completion date of September 30, 1981.

Project Officer: Janet L. Lunceford, R.N., M.S.N.

From 5/26/75 to 11/15/81

FY 81: \$100,446

Dr. Joseph W. Cullen, University of California at Los Angeles, 924 Westwood
Boulevard, Los Angeles, California 90024

Objectives: The UCLA Jonsson Comprehensive Cancer Center (JCCC) Office of Cancer Communications (OCC) has two primary goals: (1) to provide education, information and referrals, and psychosocial counseling concerning cancer for non-professional audiences and individuals with special needs; and (2) to provide and improve health professionals' access to current information about cancer. To achieve these objectives, the OCC maintains a Psychosocial Cancer Counseling (Telephone) Line (PCCL); provides current, accurate information and referrals about cancer for the lay and professional public contacting the JCCC; designs, implements, and evaluates public and patient education projects; and maintains a cancer information resource bank for the professional and non-professional communities.

Accomplishments: In meeting our objectives during this period, the OCC received 3,000 telephone calls for cancer counseling services, and information and referrals. The PCCL was expanded to meet the growing needs for that service, including development of a training and screening package for volunteer counselors. An evaluation of the PCCL was successfully completed; and promotion of this service to the professional community was increased. Other public and patient services include the following: (1) Information and referral resources, including information about new clinical research projects, continue to be updated and disseminated; (2) Bimonthly publication of the UCLA Cancer Center Bulletin, including approximately four articles per issue on cancer control, and distribution to more than 11,000 health professionals continues; (3) A one-day Breast Cancer Workshop for 200 people in the general public was held; (4) A slide-tape information program for new radiation therapy patients was evaluated, as was another slide-tape program for chemotherapy patients utilizing a hepatic arterial infusion pump; (5) Research and consultation preparatory to development of a patient education booklet on sexuality for cancer patients has been conducted.

Plans: Plans include expansion of the PCCL using a volunteer corps and evaluation of a psychosocial counseling training package for other CIS programs; development and evaluation of a patient education booklet on sexuality; continued bimonthly publication of the UCLA Cancer Center Bulletin; and continuing responsiveness to public and patient education needs.

Project Officer: Thomas Kean

Contract 85398: Comprehensive Cancer Center Communications Network - Ohio

From 9/19/75 to 11/15/81

FY 81: \$22,000 (estimate)

Dr. David S. Yohn, Suite 302, 410 West 12th Avenue, Columbus, Ohio 43210

Objectives: The Ohio Cancer Information Service (OCIS) provides the public, cancer patients and their families, and health professionals access to the most current and accurate information on cancer. Site specific as well as community resource information is available to all Ohioans through a toll-free telephone system. The Communications Network Office (CNO) provides educational programs and materials to community physicians, oncology nurses, cancer patients, and the public and implements a long-term promotional strategy for the OCIS and publishes a quarterly professional education newsletter, develops cooperative ties with other organizations and maintains the resource directory for the OCIS.

Accomplishments: The average number of calls per month from October 1980 through February 1981 is 382, an increase over last year of 17%. Since January and February 1981 have shown dramatic increases (471 and 490 calls, respectively), we anticipate achieving our goal of 600 calls per month by Fall 1981.

We aggressively promote the service through mass media, supplying fresh public service announcements, news releases, and TV slides regularly. We are furthering our relationships with other cancer-concerned organizations in the state in an attempt to increase utilization of the service by health and other professionals and possibly to develop programs cooperatively with these organizations.

The CNO has produced, in cooperation with the Cancer Control Consortium of Ohio, Inc. (CCCCO), a total of six Cancer Resource Guides covering eight counties. Seven more guides covering 16 additional counties are to be published by September 1981.

Work has begun to develop educational materials for teenage cancer patients. A committee has been formed and a proposal distributed and tentatively accepted. A needs assessment tool will be developed by the committee; the implementation of the survey will be accomplished in a cooperative effort with Children's Hospital. By September 1981, we plan to have completed the needs assessment and selected the target audience.

The public education committee is developing a proposal for identifying high risk patients for breast, colon and possibly lung cancers and providing educational materials, special screening schedules and physician counseling to them.

Plans: Our plans beyond September 1981 include: increased promotion of the OCIS among target groups; piloting the proposed public education project at OSU and, hopefully, expansion to other centers; the completion, if need is documented, of teenage patient education materials; and the continued upgrading of the professional educational newsletter.

Project Officer: Thomas Kean

From 02/16/76 to 08/31/81 FY 81: 0 (Ann. \$97,000)
Dr. J. S. Morgan, Valley View Hospital, Ada, Oklahoma 78420

Objectives: The Ada/Shawnee Clinical Oncology Program has been operational since November 1977. The objective of the Program was to deliver care to the cancer patient on a local level with the aid of on-site consultation by a radiation therapist and a medical oncologist, services not previously available in the Ada or Shawnee area. Pretreatment evaluation treatment, and post-treatment follow-up were to be upgraded by establishing management guidelines. The guidelines were established for 14 most common tumors seen. Those guidelines were to be distributed to physicians and nurses involved in the care of the cancer patient. Clinics were to be established in both hospitals so that selected patients could be followed by the radiation therapist and the medical oncologist.

Patients not followed in the clinics were to be followed by their private physicians in the community or referred to medical centers as indicated. It was hoped wherever possible to be able to treat patients locally, decreasing the necessity of inconvenient travel. Bi-monthly Tumor Board Conferences were to be utilized for entering all new cases of tumor into the Tumor Registry in both hospitals for discussing each case from a standpoint of further evaluation or disposition or enlarging upon them as an educational exercise, since the Tumor Board Conferences were well attended by staff physicians in both hospitals.

The need for the project was seen, in the fact, that prior to the implementation of the project, most patients with cancer were referred to medical centers in Oklahoma City and Tulsa for specific care other than surgery, and these referrals involved the expense and inconvenience of travel from two hours to two and a half hours per trip.

Accomplishments: On August 1, 1980 the hospitals assumed financial responsibility for the Oncology Clinics at Ada and Shawnee. Dr. Acker, continues as a radiotherapy consultant from the Oklahoma Cancer Center on a fee-for-service basis. Dr. Oldham who has served as Medical Oncology Consultant to the program has entered private practice in Ada, becoming the first such specialist in the area. Final evaluation reports and statistical analyses are being developed for submission to NCI.

Plans: The cooperative effort between Ada and Shawnee has proved beneficial to both communities and cancer patients in the region and will be maintained after federal funding ceases.

Project Officer: Donald N. Buell, M.D.

Contract 85418: Study to Determine the Feasibility of a Statewide Cancer Control Activity

From 09/29/78 to 04/30/81

FY 81: 0 (Ann. \$152,624)

Mr. Daniel J. O'Hern, Counsel to the Governor, Office of the Governor,
State of New Jersey, Trenton, NJ 08625

Objectives: This contract was awarded through the Office of the Director, NCI, to the State of New Jersey, which has exceptionally high death rates from cancer, to evaluate the feasibility of a Statewide Cancer Control Program. The contract was later transferred to DRCCA, and Dr. Sloan was designated project officer in May 1980.

The major purposes of the project were to test the feasibility of harnessing State resources, match them to community and private resources, assign responsibilities to the separate sectors, and coordinate and mount a state-wide effort of cancer control.

Under the contract, the National Cancer Institute provided staff support to the Governor's Cabinet Committee on Cancer Control to monitor agency activities and focus coordination and collaboration within State government and with the private sector. In addition, a subcontract with the New Jersey State Department of Health attempted to develop a methodology for evaluating cancer control programs.

Accomplishments: The Statewide Cancer Control Coordinating Committee, made up of representatives from each of the major government departments, was constituted soon after the award of the contract in July 1981. Dr. Ian Mitchell, who had been serving as an assistant to the Assistant Secretary for Health of DHEW, was hired to direct the staff serving the coordinating committee and was given ready access to the Governor and his staff. A general survey of all cancer control efforts in the state was carried out and special attention was devoted to the Statewide Cancer Incidence Registry, a statewide asbestos program, cervical cancer control, problems of environmental and occupational cancer, and health manpower in New Jersey.

The committee also reached agreement on responsibilities for nuclear accident preparedness, highlighted by this State's experience as a consequence of the nuclear accident at Three Mile Island in Pennsylvania in May 1979. This resulted in a successful request for legislative action assessing public utilities for the necessary funds to prepare a potassium iodide stockpile.

An interagency agreement with respect to occupational health assigned responsibility for examination of environmental health problems in the workplace to the Department of Health when requested by the employee, and to the Department of Labor and Industry when requested by the employer, and clarified the role of the Department of Environmental Protection.

Indirect accomplishments included a focus on the procedures for use and acceptance of computer programs to correlate cancer-related information such as data on water and air samples and their relevance to health statistics,

Project Officer: Margaret H. Sloan, M.D.

and an impetus to legislative banning of smoking in a variety of public places, together with the development of a Governor's program banning smoking in places of State employment.

The principal accomplishment of the contract was the demonstration that professional assistance to the political arms of government was effective in improving communication and coordination between State agencies' programs of cancer control and the public sector.

The dynamics of action of such a coordinating committee were analyzed carefully and a subcontract was awarded through competitive bid to evaluate the entire effort. The evaluation contractor's conclusion was that the committee had been reasonably successful and represented one good model of a coordinating mechanism for a State. Other models are certainly possible, and a Governor's Cancer Coordinating Committee cannot guarantee resolution of rivalries between State agencies, personality conflicts or deeply held differences in attitudes and opinions. On the whole, however, the evaluation contractor considered that the State and NCI had gained valuable information from this contract and that a Governor's Cancer Control Coordinating Committee would be worthy of consideration by other states and other governors.

A draft of the final report was approved by the project officer in February.

Plans: The Cabinet Committee, in reviewing the work of the project, strongly recommended that the Governor continue the efforts of the Cabinet Committee on Cancer Control and reinforce his original executive order. To assist the Governor and his executive staff, it is recommended that professional assistance (perhaps not as extensive as the staff during the contract period) be provided to the Governor's office to help the Governor evaluate the competing demands and claims of the several departments of State government in the area of cancer control. Plans are also under way to formulate and implement the State asbestos policy as developed by the Cabinet Committee and to follow up on the State's public health concerns in the field of nuclear accident preparedness and the disposition of chemical waste.

The contract terminated on April 30, 1981.

From 09/30/78 to 06/30/82

FY 81: 0 (Ann. \$265,076)

Dr. Leah Ziskin, New Jersey State Dept. of Health, Trenton, New Jersey
08625

Objectives: This project seeks to reduce cervical cancer mortality and the progression of early detected cervical cancer morbidity in New Jersey by providing cervical cancer screening services to high risk women. Secondly, this project hopes to test and demonstrate a model of secondary prevention of cervical cancer in selected sites incorporating a method of outreach which relies heavily on the enlistment of peer opinion leaders in the target population, as well as screening, diagnosis, short and long-term follow-up, patient education, and the involvement of community facilities in treatment and rehabilitation of cases discovered. Thirdly, as a long-range objective, we seek to encourage the establishment of ongoing screening programs supported jointly by community resources, third-party payers, and the State Health Department resources.

Accomplishments: As of March 31, 1981, approximately 15,405 women have been screened in this project. Three selected laboratories continue to process all initial Pap smears and quality control mechanisms continue to be implemented to correlate the cytological with the pathological diagnosis of each non-negative Pap smear. Of the number screened, 435 cases of dysplasia or precancerous abnormalities involving the cervix of the uterus, seven cases of carcinoma in situ, six cases of invasive carcinoma, and seven cases of other gynecologic neoplasia have been found on the initial Pap smear. Follow-up has been initiated on all of these women and agreements continue with eight hospitals with American College of Surgeons approved cancer control programs for the provision of definitive diagnostic services. In early 1980, a cervical cancer update session was held for all screening agencies. The purpose of this meeting was to reinforce the objectives of this project, update all agencies to the current status, and plans for the future, review some interesting cases and discuss common problems and specific outreach, tracking and follow-up modalities which have proven successful in the first year of operation.

Plans: Efforts will be made to screen an additional 26,000 high risk women from this point to the completion of the project. Agencies will be encouraged to develop mechanisms for the continuation of this project after June of 1982. Physicians and diagnostic referral centers will continue to be encouraged to implement the standardized medical protocols developed by the Department.

Project Officer: Robert T. Bowser, Ph.D.

Intraagency Agreement 90606: Joint Food and Drug Administration/National
Cancer Institute Radiation Quality Assurance
Programs

From 10/01/80 to 09/30/81

FY 81: \$150,000

Mr. Ronald Jans, Bureau of Radiological Health, Food and Drug Administration,
5600 Fishers Lane, Rockville, Maryland 20857

Objectives: To assure safe and efficient use of radiation in the diagnosis and treatment of cancer and other diseases through the support and conduct of radiation quality assurance programs. These programs allow health care facilities to (1) reduce unnecessary radiation exposure of patients and, consequently, the potential for radiation induced cancer or other ill health effects; (2) improve quality for better diagnoses; and (3) improve the quality of care in radiation therapy.

Accomplishments: Major accomplishments have been achieved in six areas. First, radiological health agencies continued to implement the mammography quality assurance program known as Breast Exposure: Nationwide Trends (BENT). Approximately 200 mammography facilities were screened with thermoluminescent dosimeters and States used the BENT survey technique to evaluate facilities during routine inspections. Since this program began in 1976, 47 States and 13 other radiation control agencies have surveyed over 80 percent of the mammography units in the United States. More than one-half of these units have been resurveyed, demonstrating a 27 percent exposure reduction (10 to 15 percent reduction in dose). Second, in order to address problems identified in the BENT program, a working group of nationally recognized mammography experts completed collection of data on an evaluation of mammography imaging phantoms. The report of the group is being used to assist physicians and physicists in identifying and correcting mammography imaging problems. Third, cooperative relationships have been established with the Centers for Radiological Physics in the areas of chest radiography, computed tomography, and radiation therapy. Joint production of survey protocols, training and educational materials is intended to enhance capabilities and effectiveness of consulting physicists and radiation control programs. Fourth, several videotapes were produced, addressing the topics of brachytherapy and medical linear accelerators. An introductory level publication on the theory and operation of medical linear accelerators, complementing the videotapes, was published. The script for a training package on Radiation Therapy in the Treatment of Skin Cancer was finalized and production begun on art work for the slides. Fifth, contractors delivered a first draft of quality assurance training materials for radiation therapy technologists, as well as a revised calibration protocol for photon and electron beams used in radiation therapy. Sixth, national symposia were conducted on Computerized Treatment Planning and on Computed Tomography in Radiotherapy.

Project Officer: Winfred F. Malone, Ph.D.

Plans: Activities in quality assurance for mammography, computed tomography, chest radiography, and radiation therapy are continuing. The training materials for radiation therapy technologists will be reviewed by a consultant panel of nationally recognized experts in October and a pilot workshop will be held in December, 1981. The final document will be published and promoted in FY 82, along with 1) the report of the working group on mammography phantoms, 2) the revised calibration protocol, 3) the publication on medical linear accelerators, and 4) the proceedings of the two symposia. Future plans also include production on various educational materials and workshops on specific quality assurance problems.

From 07/01/79 to 09/30/82 FY 81: \$74,000 (estimated)
Mrs. Dorothy Rice, National Center for Health Statistics, Center Building
Hyattsville, Maryland 20782

Objectives: The objective of this project is to carry out a series of methodological surveys in order to develop a final protocol for a proposed national survey of the cost of cancer care. A national survey would provide needed estimates of cancer care costs such as: (1) accurate estimates of the financial burden borne by cancer patients and their families, (2) estimates of the differences in costs to patients and to society for early versus late diagnosis of the disease, (3) estimates of the effect on costs of different treatment and rehabilitation interventions, and (4) the relationship of cost to socioeconomic and demographic variables, institutional and provider variables, and clinical variables.

Accomplishments: The methodological experiments which are being conducted in this pilot study are designed to evaluate the potential effectiveness of network sampling as an alternative sampling procedure for identification of a national sample of cancer patients and to test alternative methods of collecting detailed medical, health care services utilization, and cost-of-care data from cancer patients. In the pilot study, households of known cancer patients comprise about two-thirds of the study sample. Network sampling allows cancer patients to be identified at their own households and at households of close relatives. The effectiveness of this method depends on the ability of close relatives to report the relative with cancer, and on the willingness of cancer patients to report their own conditions. In January 1981, the first stage of the pilot study was completed which involved field testing a supplement to the Health Interview Survey questionnaire which queried households about household members and close relatives with cancer.

Cancer patients identified in their own households in the first stage were contacted again three months later to take part in a panel study to collect medical care cost and utilization data. The first round of panel interviews has been completed, and the second and final round will be carried out in April and May of this year.

A medical provider follow-up to verify the diagnosis, costs, and utilization reported by cancer patients will be carried out in the fall of 1981.

Plans: Results of the three stages of the study--the household survey, the panel study, and the medical provider follow-up--will be evaluated in terms of the effectiveness of these methods for a National survey of cancer care costs. If the methods prove effective, a design protocol will be developed for applying the strategy in a National survey.

Project Officer: Jan M. Howard, Ph.D.

Contract 95417: Pain Control in Cancer (Chicago)

From 09/28/79 to 09/27/82

FY 81: \$116,000

Dr. Robert G. Addison, Rehabilitation Institute of Chicago, 345 E. Superior Street
Chicago, Illinois 60611

Objectives: Multidisciplinary approaches to management of chronic pain have been successful in certain clinical problems such as low back pain and chronic pain, but have not been systematically evaluated in cancer patients. The objectives of this project are: (1) to establish a multidisciplinary pain management team for the evaluation and treatment of patients with pain directly related to their cancer or its treatment, and (2) to determine if pain control for these patients is best managed by a program of early evaluation and treatment by this type of team.

Accomplishments: This study is a collaborative effort and our first accomplishment has been the development of a common protocol to be used by all seven participating centers. Common study design, patient entry criteria and test instruments have been decided on. Test instruments have been precoded for computer entry and a study manual, hypotheses and secondary observations have been written.

At this institution a multidisciplinary team of physicians and other health care professionals has been developed specifically for the evaluation and treatment of cancer patients with pain. The team is functioning successfully and meets regularly to establish pain management plans for the patients that are referred to the program and are randomized for the study group. These plans are then recommended to the attending physician for implementation.

The study is being publicized at departmental conferences and at rounds and in-patient oncology units in a continued effort to recruit patients. Patient accrual has been steady and compares well with the accrual rate of other participating institutions. Data collected from the patients in the study will be pooled with the data from other sites.

Plans: At the completion of this project we will have acquired sufficient information from the patients entered into the experimental group and the control group, at the seven participating centers, to begin testing the objectives. Data will be analyzed to determine the effectiveness of the pain management team approach of dealing with cancer pain. Guidelines for the evaluation and management of pain in cancer patients will be written, along with a final collaborative report.

Project Officer: Donald N. Buell, M.D.

Contract 95419: Development of an Informational Data Base for Public Health Strategies in Cancer Prevention

From 10/30/79 to 09/29/81 FY 81: \$170,000 (estimated)
Dr. A. F. Meiners, Midwest Research Institute, 425 Volker Boulevard,
Kansas City, Missouri 64110

Objectives: The objectives of this program is to assist NCI with its responsibilities in gathering and organizing information on the prevention of chemical carcinogenesis and in transferring this information to occupational and environmental health professionals, the health care delivery system, and the public.

Accomplishments: After consideration of about 400 chemical carcinogens, 89 compounds were selected for critical examination with regard to: (a) what is known concerning human carcinogenicity at the present time, (b) the present potential for human exposure in the workplace, from consumer products, and through the environment, and (c) the possibilities for prevention and reduction of exposure.

The information concerning the 89 compounds was summarized in a 3-volume set of dossiers entitled "Chemical Carcinogen Dossiers, A Contribution to the Data Base for Cancer Prevention," (948 pages total). Two special reports were prepared concerning these carcinogens. The first was a summary of the available epidemiological evidence for 43 of these carcinogens that appeared to be of greatest concern. The second, entitled "Selection of Carcinogens for Cancer Control and Prevention Programs," described the selection of seventeen carcinogens for more intensive review and assessment of methods and strategies for preventing and reducing human exposure.

These seventeen carcinogens were selected on the basis of (a) evidence for human carcinogenicity, (b) extent of exposure, and (c) feasibility of exposure preventions strategies. They are: Ethylene Oxide, Aflatoxins, Acrylonitrile, Carbon Tetrachloride, Polychlorinated Biphenyls, Beryllium, Beryllium Oxide, 1,2-Dichloroethane, Phenacetin, p-Dioxane, Bis(chloromethyl) Ether, Chloromethyl Methyl Ether, 1-Naphthylamine, 2-Naphthylamine, Direct Black 38, Direct Blue 6, and Direct Brown 95.

Plans: Exposure prevention documents covering these carcinogens are presently being prepared: these documents are intended to provide information for a diverse audience (including public, occupational and environmental health professionals, other members of the health care delivery system, public health educators, labor and consumer groups, and the general public) concerning the possible risks of exposure to the subject chemical and the available options and strategies for reducing these risks. The documents will contain information concerning (a) production, distribution and use patterns, (b) health hazards, (c) sources and levels of human exposure, and (d) exposure and reduction strategies (including specific control measures, education and medical surveillance).

Project Officer: Winfred F. Malone. Ph.D.

Contract 95428: Development of a Model Post-Master's Fellowship Program in
Oncology Nursing Education

From 9/20/79 to 9/29/83

FY 81: \$190,000

Dr. Anne Belcher, University of Alabama, Birmingham, Alabama 35294

Objectives: The purpose of this program is the graduate level preparation of nurse educators which will enable them to plan, implement and evaluate curricula in oncology nursing at the undergraduate, master's and/or continuing education levels in their employing institutions. It is anticipated that the students of these educators will function in a variety of health care agencies, providing care to individuals with cancer, to their families, and to the community. Recommendations for future programs in oncology nursing education will result from this project.

Accomplishments: The specific activities of the project which have been achieved since October 1, 1980 are as follows:

1. Approval of the curriculum for the program at all levels within the School of Nursing.
2. Finalized negotiations for fellows' preceptored clinical and educational experiences.
3. Admission of four (4) fellows into the program.
4. Implementation of sequenced course of instruction to meet program objectives.
5. Continued national publicity coordinated by NCI through the University of Alabama School of Nursing's public relations office.
6. Revision, printing and distribution of a program brochure for University of Alabama at Birmingham (UAB) and San Jose University Department of Nursing (SJSU).
7. Continued development of a common plan for outcome evaluation of program with SJSU.
8. Utilization of modified "task analysis" approach for process evaluation.

Plans:

1. Continued work with SJSU on plan for outcome evaluation of program.
2. Continued publicity and recruitment efforts.
3. Exploration of plans which need to be developed for continuance of program.

Project Officer: Janet L. Lunceford, R.N., M.S.N.

Contract 95432: Smoking Cessation Intervention for Special At-Risk
Populations

From 09/28/79 to 09/27/82 FY 81: \$54,628
Dr. Virginia Li Wang, Johns Hopkins University, Baltimore, Maryland
21205

Objectives: The purpose of the study is to evaluate the effectiveness of a multi-component approach to smoking cessation involving individualized patient and physician educational efforts. The rationale of the study approach is twofold: (1) Variations in smoker's characteristics require differential cessation approaches to confront smoking problems on an individual basis, and (2) the physician could be most effective in motivating patients to stop smoking by imparting specific information related to that individual's smoking risks.

Accomplishments: This project has developed and implemented a smoking cessation intervention program with asbestos exposed shipyard workers involving physician-smoker encounter during routine care. A physiologic, behavior and knowledge profile of the population has been obtained. Data source included spirometry and x-ray results from medical records, and smoking history practices, attitudes and knowledge by means of a self-administered questionnaire.

The intervention involved training primary care physicians to deliver a standardized counseling protocol to the workers with individualized physiologic and symptom assessment incorporated into a brief message. Physicians counseled the smokers on a cold turkey method of quitting and asked for a commitment to a quitting target date. Smokers were divided among exposed and control groups with both normal and abnormal lung functions.

Three-month follow up by telephone has been completed. One-year follow up is currently underway with carbon monoxide verification. A medical record review is being undertaken with an additional 3,000 workers at the shipyard who have had a smoking history in order to determine spontaneous cessation rates and smoking pattern.

Plans: Conduct one year follow up and analyze effects. Write final reports and scientific papers.

Project Officer: Catherine S. Bell, M.S.

Contract 95433: Develop Course on Prevention, Focusing on Cancer for
Physician Assistants

From 9/19/70 to 9/17/82

FY 81: \$77,800

Mrs. Suzanne Greenberg, Northeastern University, College of Pharmacy and Allied
Health Professions, 360 Huntington Avenue, Boston, Massachusetts 02115

Objectives: The purpose of the course is to teach physician assistants (PAs) principles of prevention with a focus on cancer and to evaluate critically and integrate into practice research findings regarding prevention. Specific goals include increased awareness of possible cancer-producing agents and conditions, understanding of legal issues in prevention, ability to select appropriate resources for prevention and detection, and ability to encourage behavior change in patients.

Accomplishments: A faculty was assembled in the fall of 1979 to plan the course objectives. Subsequently, detailed course objectives were prepared for each topic. In the spring of 1980 the faculty presented lectures or written texts for each topic. Lectures were videotaped, and three written modules were used in a pilot run of the course. In the fall of 1980 the objectives were revised. Using the taped lectures and written modules as a resource, faculty redesigned the course and prepared seven self-study packets entitled:

1. Epidemiology and Biostatistics
2. Cancer Biology
3. Occupational and Environmental Cancer Risks
4. Regulatory and Legal Procedure to Prevent and Remedy Exposure to Carcinogens
5. Patient Health Education
6. Clinical Evaluation of the High Risk Patient
7. The Role of the Laboratory

The revised course also includes four videotaped lectures or discussions, a set of videotaped vignettes to trigger discussion on patient health education, a slide-tape presentation of risk factors, and outlines for "live" presentations or discussions. A series of objective examinations was prepared based on the trial use of items in the 1980 pilot run. There is now one examination for pre- and post-testing and three quizzes. Two attitude instruments have been used to measure attainment of affective objectives.

Plans: The course will be field tested at three sites in the spring of 1981. The sites are Northeastern University, Wichita State University, and Mercy College. The course will be packaged for replication by other schools.

Project Officer: Arlene R. Barro, Ph.D.

From 9/28/79 to 9/27/82

FY 81: 71,900

Dr. Richard Love, University of Wisconsin Clinical Science Center,
600 Highland Avenue, Madison, Wisconsin 53792

Objectives: Although cancer prevention services provided in the primary care setting could result in the reduction of cancer morbidity and mortality in the American population, clinical preventive oncology is not taught to physicians-in-training in medical schools or residency programs. Based on the precept that alterable factors in cancer causation are consequences of physician and/or patient behavior, a 12-module/24-hour classroom course is being designed to advance knowledge and skills in cancer prevention which have direct application in clinical practice. Curricular goals include the definition and presentation of: (1) a cancer risk factor identification strategy, (2) risk factor reduction or elimination approaches, and (3) elements of the practice of and strategies for secondary prevention.

Accomplishments: The development, field testing, and evaluation of the clinical preventive oncology course is a joint effort of a seven member working group of University of Wisconsin faculty representing the Departments of Human Oncology, Psychology, Family Medicine and Practice, Preventive Medicine, and Educational Resources. Since the initiation of the project October 1, 1979, the group has developed a 450-page syllabus including instructional objectives, student performance criteria, learning activities, and readings for the 12 modules. Teaching materials and methods are being developed and field tested, including stop-action videotapes, case presentations, interactive exercises in history taking and self-critiquing, posters suitable for office patient education, and patient/physician education resources. To accomplish formative and summative evaluation of the course, a cancer attitude inventory and knowledge/skills examinations have been composed, piloted, field tested, and revised. By June 1, 1981, the course will have been presented to 80 Family Medicine residents at six Department of Family Medicine and Practice statewide residency program clinics. In September of 1981, the course will be field tested with fourth year medical students. During the academic year 1981-1982 the course will be field tested (and final revisions made) with 90 residents at the Medical College of Wisconsin programs in Family Medicine. The working group members are responsible for course modules as follows: I. Critical Concepts in Cancer Causation, Richard R. Love, M.D. (Medical Oncology). II. Critical Concepts in Cancer Prevention, Howard Leventhal, Ph.D. (Psychology, Medical Sociology). III. Critical Concepts in Cancer Screening, Dr. Love. IV. Case-Finding for Breast, Colorectal, Lung, and Cervical Cancers, Dr. Love. V-VI. Smoking, Dr. Leventhal. VII. Diet, Marion Field Fass, Sc.D. (Patient Education). VIII. Occupations, Jay Noren, M.D., M.P.H. (Preventive Medicine). IX. Environmental and Radiation Factors, Dr. Noren and Jon K. Sternburg, M.D. (Family Medicine). X. Clinical Decision Making for Cancer Risk Reduction, Dennis Fryback, Ph.D. (Preventive Medicine and Industrial Engineering). XI. Genetics, Dr. Love. XII. Cancer Prevention in Clinical Practice--Strategies (Drs. Sternburg, Fass).

Project Officer: Arlene R. Barro, Ph.D.

Plans: Contract work until completion of the project's third year will include completion of course field testing, analysis of evaluation data, course revision, creation of course description documents, development of teachers' instructions, and the writing of a journal article describing course development. The course will be packaged for replication by other schools.

Contract 95435: Professional Education in Cytology of Bladder, Lung,
Colorectal and Cervical Cancer

From 09/30/79 to 09/29/82

FY 81: \$130,000

Dr. E. Barker, University of Washington, Harborview Medical Center, 325
Ninth Avenue, Seattle, Washington 98104

Objectives:

- a. To increase the awareness of the utility and latest concepts and procedures in exfoliative cytology in early detection or diagnosis of cancers of the lung, bladder, uterine cervix, and colon/rectum, supplemented by material from aspirates from thyroid and other accessible tissues.
- b. To increase the competence of cytotechnologists and cytopreparatory technologists in preparing cytological material for microscopic examination.
- c. To update and increase the expertise of at least 250 cytotechnologists and 50 cytopathologists in the interpretation of cytological specimens derived from the sites under discussion, during the three year period.
- d. To develop and help maintain a good working rapport in the broad Northwest region among the clinicians and their consulting cytopathology laboratories, and among the laboratories in the region.
- e. To establish and continue a viable quality assurance program for cytology in the region.

Accomplishments: The contractor has prepared: modules of instruction in urinary, respiratory, colorectal, and cervical cytology; supplementary modules of instruction in aspiration cytology and in laboratory effectiveness; and appropriate examination and review materials for each of the above teaching modules.

The contractor has prepared and used a scientific/educational exhibit for display at medical society meetings in the Pacific Northwest; and presented a dozen in-depth workshops by September 30, 1981: half in cities across the state of Washington, and others in Oregon, Montana and Hawaii; Alaska, Idaho and Wyoming are being surveyed for potential workshops.

Plans: The contractor plans to present the appropriate workshop and follow-up procedures to at least twenty (20) groups before the end of the contract. In the first ten workshops, 180 trainees included cytotechnologists and pathologists from scattered other states as well as from Washington, Oregon, Idaho, Montana, Wyoming, and Hawaii. The program is improving the awareness, competence, and quality of the cytopathological professional community, as well as informing the practicing clinicians of the importance of exfoliative cytology in the early diagnosis of cancer and helping to develop a rapport among the clinicians and their consulting cytopathology laboratories within the region. Clinical groups are helping to secure good case material.

Project Officer: Chauncey G. Bly, M.D., Ph.D.

Contract 95437: Cervical Cancer Screening Program Data Support Project

From 04/01/80 to 04/01/81

FY 81: \$575,005

Mr. M. Cohen, Evaluation Technologies, Incorporated, 2020 N. 14th Street,
Arlington, Virginia 22201

Objectives: The Cervical Cancer Screening Demonstration Program was implemented seven years ago to promote mass (Pap smear) screening of high-risk women. Since that time, 32 states have had contracts with NCI to obtain Pap smears and follow-up information. The goal was to provide three annual smears for women who had not been examined during the previous year. Definitive diagnoses were afforded those women showing abnormal cytology, and assistance was provided for an entrance into the medical care system. Each screening, biopsy and treatment encounter was recorded on a Unit Screening Report and stored at a centralized data center. A major objective of the program remains to analyze and interpret the contents of the data base which contains data on more than one million women.

Accomplishments: During this reporting period, 7,596 smears, 112 biopsies, and 19 treatments were recorded for the state of New Jersey which will remain an active participant through FY 81. Data conversion was completed for three states; Wyoming, Hawaii and Maryland, and, a computerized comparison was made between unconverted and converted data. Numerous computer programs were created to analyze the data base and two research papers resulted from the analyses. One paper concerns the demographic characteristics of the program participants in relation to initial smear outcomes. Another paper concerns the observed disease history modeled as a Markov Chain and the natural disease history as extracted from the observed history. The issues of false test rates, disease regression, and disease recurrence are discussed. Two states, Arkansas and Alabama, have contributed additional data to the national program consisting of encounter data, demographic data, and risk factor data collected over a ten-year period. These data will allow the refinement and extension of analytical techniques currently in use.

Plans: The primary focus of the program will be on data interpretation and dissemination of results to the scientific community. The analyses show promise and will be presented to working groups of various disciplines for critical review. An effort should be made to upgrade and expand the data base using data already collected from numerous states. A recent survey conducted by NCI indicates that a vast amount of encounter information can be captured from states which continued Pap screening after the Demonstration Program was terminated.

Project Officer: Robert T. Bowser, Ph.D.

Contract 95438: Development of Protocols for Worker Notification and Information Programs

From 09/30/79 to 09/29/81

FY 81: 0 (Ann. \$114,000)

Dr. P. L. Polakoff, Western Institute for Occupational and Environmental Sciences, Inc., 2520 Milvia Street, Berkeley, California 94704

Objectives: The objective of this project is to identify communication channels to provide notification and information to workers about exposure to carcinogenic substances in the workplace. Specific tasks include the following: (1) to determine the specific organizational and communication characteristics of the occupational setting involved; (2) to identify the communication systems of the workplace and the community engaged in notification/information programs; (3) to identify potential methods and channels of communication for reaching exposed individuals who are no longer employed where exposure occurred; (4) to plan and design an effective worker N/I program; (5) to prepare and validate notification and information protocols for auto repair workers and firefighters.

Accomplishments: Ongoing working relationships have been established with two union locals. Collection of data on the organization and communication channels of both the unions and the workplace has been completed. A survey of union members regarding attitudes toward health, their knowledge of occupational carcinogens, and their trust and distrust of health information sources has been completed. Research on carcinogenic exposures in fire-fighting and auto repair work, and on legal aspects of worker notification has been completed. Joint committees consisting of the program staff and representatives of the local unions have planned the worker notification and information programs to be conducted in May and June 1981. Notification letters, pamphlets on asbestos and other carcinogens, and follow-up services have been developed by the joint committees. Community agencies providing services and other resources to persons with occupational cancers have been alerted to notification plans. A conference on the ethical issues of worker notification will be held in June 1981.

Plans: Summary reports on the survey questionnaire data will be prepared. Notification programs will be analyzed and evaluated for effectiveness. The protocols will be written, based on an evaluation of all of the above specific activities and on the survey questionnaire results. Future plans also include an evaluation of the entire project, the development of a model program for nation-wide application, further cooperation and participation by management in the project, and the completion of legal research and analysis of worker notification.

Project Officer: Andrew F. Hegyeli, D.V.M., Ph.D.

Contract 95439: Design and Evaluation of Cancer Education Protocols

From 9/28/79 to 9/27/82

FY 81: \$169,000

Dr. Virginia Li Wang, The Johns Hopkins University, School of Hygiene and Public Health, Baltimore, Maryland 21205

Objectives: This proposal develops and tests health education protocols and programs in a variety of settings. The areas addressed are: (1) smoking cessation in family planning clinics, (2) breast self-examination in a student health service, and (3) occupational school health education. The project utilizes a diagnostic framework to develop and evaluate models in which to organize the experience, theory and research surrounding health education as to make it transmittable and replicable. The protocols will be tested in relation to several different cancer sites to determine its generalizability and to describe the variations required in the different settings.

Accomplishments: Family Planning Clinics - Four educational elements were defined for implementation in four urban public Family Planning Clinics. Educational and data collection instruments were prepared, providers trained, and OMB Clearance obtained. Educational components designed include: a Smoker's Self-Assessment Questionnaire (SAQ); a Self-Help Guide pamphlet (SHG); an audiovisual package (AV) consisting of a film and set of 5 specially designed waiting room posters targeted to the population: a 2-3 minute individualized quit smoking message (PrMess) delivered to the woman by the examining care provider, CNM or MD. These are combined into the following "minimal intervention" treatment strategies being tested in a pre-test/post-test design: (1) SAQ+SHG; (2) SAQ+SHG+AV; (3) SAQ+SHG+PrMess; (4) SAQ+SHG+AV+PrMess. Fifty-eight percent of anticipated sample size of 1606 female smokers have been recruited for participation. Three-month preliminary follow-up results on 426 women reveal substantial quit rates varying by intensity of intervention (from 8% in SAQ group to 20% in provider message group).

Breast Self-Examination - The University of Maryland at College Park was chosen for site demonstration. Two major phases of the project include: (1) educational diagnosis and (2) intervention and evaluation. Baseline diagnostic surveys were conducted on 600 students and 90 mothers. Measures of performance: frequency, regularity, range (number of positions and type, number of minutes) and thoroughness (what is done in each position) were obtained as well as information on predisposing (e.g. awareness, knowledge, attitudes), enabling (e.g. privacy), and reinforcing (e.g. exposure to BSE messages) factors. Analyses of the surveys were used in the final development of the educational intervention program. The intervention program runs approximately 50 minutes and includes cognitive and affective materials as well as skill development material. Educational materials for the program include: (a) handouts; (b) pamphlets; (c) seal-back stickers; (d) a film; (e) breast teaching model; (f) modeling; and (g) other audio-visual aids. Student peer facilitators were selected and trained. The intervention programs were conducted by the peer facilitators in three settings: (1) classes; (2) informal workshops; and (3) intensive community program (BSE clinic). Pre-intervention data were obtained from appropriate experimental groups. Experimental and control groups will be followed up at six months post-intervention.

Project Officer: Arlene R. Barro, Ph.D.

Occupational School Health Education - The Baltimore City Public School system was selected as the demonstration sites for the occupational cancer protocol project. There will be two target populations: (1) high school students, and (2) vocational-technical school students. The project is divided into three interrelated activities: (1) an organizational infrastructure for implementing, maintaining and evaluating the program, which has been conducted; (2) content development to adapt for use in school programs, the state of the art in occupational cancer, from which the curriculum is now being written in final form; and (3) observational studies which form the basis for measures of behavioral change related to carcinogens and their identification. A sample of approximately 600 general high school students and some 100 students in the vocational-technical schools are to be followed for six months to assess changes in knowledge, beliefs, attitudes, and behaviors.

Plans: Implement the protocols. Analyze the specific effects of the various protocols. Integrate the protocols. Review of protocols by an expert panel and community groups. Printing of protocols in four sets, each representing a handbook or manual for cancer education in urban areas. Dissemination of manuals through professional channels.

Contract No. 95442: Identification of Effective Cancer Control Promotion
Approaches Directed to the General Public.

From 9/28/79 to 2/27/81 FY 81: None (Ann.\$105,000)
Dr. Harold Mendelsohn, University of Denver
Denver, Colorado 80208

Objectives: This project seeks to review, analyze and compile various approaches used in selected public dissemination campaigns in cancer control and other health areas and to identify and develop effective ideas, methods, techniques and principles that can be utilized or adapted in cancer control promotion efforts. The main product will be a conveniently organized compendium of principles, guidelines and examples based on theory and practice and written in lay terms that will assist policy makers and communicators in planning and implementing effective cancer control information transfer strategies.

Accomplishments: 1. An extensive bibliography has been produced that cites more than 1,000 contemporary works (1965-1968) pertaining to the theoretical basis of communicating to the public in cancer control and other health areas. Arranged by category, the bibliography establishes a reference base of what is known from theory and research in 9 communications-related areas. Included are: the Health Belief Model as related to source credibility, fear arousal, and motivation; public information health efforts; public attitudes and opinions concerning cancer and other health phenomena; epidemiology, symptomology of prevention and control in specific health areas; specific mass communications persuasion theories; general mass communications approaches; theories, issues and models of health care; health education, objectives and programs; general campaigns and mass communications effects (non-health).

2. A major accomplishment of the project is the development of an analytical monograph discussing a new strategy for effective communications in the health field. Rooted in the implications of the reference base plus perceptions of the Health Belief model, the strategy seeks to segmentalize target audiences according to their beliefs concerning vulnerability to illness and benefits to be derived from compliance. Major thesis is that in order to take preventive health actions, healthy individuals must assume the sick role.

Plans: The work done provides one link between social science theory and research and the practice of health communications. Being planned is the adaptation of what was learned in the study to the operational problems and needs of communications and health education professionals.

Publications: Mendelsohn H: Compliance and Rejection: Psychological Strategies for Effective Public Communications on Behalf of Health; in Proceedings of the Conference on Health Education and the Media, The Scottish Education Group, University of Strathclyde, Glasgow. pp 1-16, in press.

Project Officer: Adele H. Nusbaum

From 09/28/79 to 09/27/84 FY 81: \$586,340
Dr. G. Foradori, Data Management and Analysis Center For Long-Term
Follow-up, 3624 University City Science Center, Philadelphia,
Pennsylvania 19104

Objectives: To complete the development of all systems necessary for following up on approximately 65,000 participants for follow-up selected from the Breast Cancer Detection Demonstration Project. To assist in the training of all clinical follow-up personnel in interviewing and the completion and handling of questionnaires. To computerize and otherwise process all form sets completed by September 30, 1981. To provide monthly and Ad Hoc statistical reports to the NCI Project Officer for the monitoring and control of all follow-up activities. To provide the necessary liaison and coordination required to resolve problem areas and to collaborate with the NCI Project Officer in their resolution. To support epidemiological research activities as directed by the NCI Project Officer.

Accomplishments: Manual editing of forms, keying, microfilming and storage are all progressing smoothly. Data quality control and performance systems have been developed and found to be adequate . The DMAC staff participated in a training session for interviewers and coordinators from the projects funded to conduct the interviews. Several reports have been generated by the DMAC from the data received from the projects. These reports will provide feedback to the projects as to what has been submitted and provide a system of monitoring for the NCI staff. One report lists participants for whom an annual interview form has been received but no Baseline form. Beginning in May 1981, project performance and monitoring reports were generated for data received thru April 1981. Since January 1, 1980, 30,900 form sets had been submitted from the interview projects to the DMAC documenting the current status of women in the study. Upon receipt, these forms are manually edited to identify any problems in the completion of the forms. Monthly progress reports are submitted to the NCI. As a part of the liaison function, site visits have been made to 10 projects to provide assistance in the conduct of the project. Only NCI-approved requests for data and/or analytical support for potential users of the data base will be provided as the requests occur.

Plans: Because of the unique relatedness and interdependence of the data base for the BCDDP and the Long-Term Follow-Up, a modification to this contract is being processed to add tasks to the statement of work to complete all tasks, submit all deliverables, and provide continued support for collection of data from the ancillary studies and the Data Management Advisory Group recently established to guide appropriate analyses of the large screening data base. This project will be continued until the Long-Term Follow-Up Study is completed.

Project Officer: Richard D. Costlow, Ph.D.

Contract 95446: Approaches to Cancer Patient Management: A
Synopsis of the Networks (Head and Neck Cancer)

From 09/28/79 to 07/31/81 FY 81: 0 (Ann. \$148,000)
Dr. Richard B. Warnecke, Illinois Cancer Council, 36 South Wabash
Avenue, Chicago, Illinois 60603

Objectives: The purpose of this project is to produce a monograph describing the development and experiences of seven networks of hospitals and physicians established throughout the country. These networks were contracted to demonstrate and provide comprehensive state-of-the-art management for head and neck cancer patients. By exploring both the positive and negative experiences of these programs and delineating common patterns of organization among them, the monograph will serve as a reference to persons who wish to establish networks of a similar nature.

Accomplishments: This project was initiated on September 28, 1979. The major accomplishments up to July 1980 were data collection and an extensive review of literature using current organizational theory as a framework. The data collection activities pursued for each of the six networks that functioned for the duration of their contract periods were:

1. The collection of a complete set of documents and materials each network produced over a five-year period
2. The development of an interview protocol for an on-site visit of each network
3. The completion of on-site visits to the networks
4. A survey concerning shared services and staff of the chief executive officer at every hospital participating in each network
5. The collection of secondary data to provide additional information about each network region

The first and last data collection activities were performed for the seventh network which terminated after two years of funding.

Once all the data were assembled, the major accomplishment of the last half of the project was integrating the wealth of information and preparing the first draft of the monograph. Detailed case histories of each network, approved by the respective principal investigators, and an analysis of their development, following an explicated conceptual framework and based upon the case histories, comprise the monograph. The draft was submitted for review by the project officer on April 1, 1981.

Plans: The monograph has yet to be finalized. This is planned upon receipt of recommendations and suggestions generated by the review.

Project Officer: Rosemary Yancik, Ph.D.

Publications:

Warnecke, R.B. and Fennell, M.L. "Network Organizations for the Delivery of Complex Care: A Problem in Process Evaluation." In Flood, A.B., and Cockerham, W. (Eds.): proceedings of The Sociology of Health Care: Issues for the 1980s (Forthcoming).

Fennell, M.L. "Health Organizations and Their Environments." In Flood, A.B., and Cockerham, W. (Eds.): proceedings of The Sociology of Health Care" Issues for the 1980s (Forthcoming)

Contract 95450: Health Effects of Carcinogenic Exposure: A Community Demonstration Project

From 09/30/79 to 09/29/82

FY 81: \$300,000

Dr. P. L. Polakoff, Western Institute for Occupational and Environmental Sciences, Inc., 2520 Milvia Street, Berkeley, CA 94704

Objectives: The main objective of the Bay Area Asbestos Awareness Project (BAAAP) and its Resource Center is to develop information and education programs on asbestos for asbestos-exposed workers, labor and community organizations, concerned lay persons, industry, physicians and other health care providers in the greater Bay area. Specific historical, clinical, legal, economic and social determinants and effects of asbestos exposure will be identified and integrated into the program.

Accomplishments: The project and Resource Center activities are at the implementation midpoint. To date, the Center has provided two of its three planned continuing medical education seminars for physicians and other health care providers. One hundred and forty pulmonary specialists, radiologists and pathologists have attended the seminars on the clinical manifestations and treatment of asbestos-related diseases. Very shortly the Center will conduct a similar but more comprehensive forum for health care providers in the targeted community. A Center Speakers Bureau has been developed and project staff has provided speakers to and participated in over 125 community information programs regarding asbestos exposure and other occupational/environmental health issues. Over 500 asbestos (toll-free) phone line inquiries from exposed workers and family members, medical and legal service providers and organizations from around the country have been logged. The Center has received over 600 visitors, written and general telephone inquiries from the public and community agencies concerned about job and environmental health hazards, and requests for Center services. The Center has published two issues of its quarterly newsletter, the Asbestos Newslite, focused particularly for present and past-exposed workers and their families. Circulation has reached over 11,000 with increasing requests from many organizations for printing additional copies for their constituencies. The Center will soon conduct a community forum that focuses on policy issues pertaining to occupational cancer prevalence and prevention in one of the project's target counties, an area with a heavy petrochemical base.

Plans: Other planned activities include: a workshop to address the ethical, legal, economic and sociological issues with respect to notification programs for those exposed to toxic substances; a community forum for asbestos-exposed workers, retirees and their families for purposes of updating their knowledge regarding the medical, legal and scientific aspects of asbestos-related disease; and continuation of Center outreach services.

Publications: Polakoff, P.L., and Berliner, E.R.: A Community Based Occupational/Environmental Cancer Center. International Symposium on Prevention of Occupational Cancer, Helsinki, Finland, 1981, Proceedings (in press).

Project Officer: Andrew F. Hegyeli, D.V.M., Ph.D

Contract 95455: A National Correspondence Course on Lung Cancer and
Asbestos-Related Pulmonary Disease

From 09/20/79 to 08/01/81

FY 81: 0 (Ann. \$38,450)

Dr. Alfred Soffer, Executive Director; Dale E. Braddy, Director of Education,
American College of Chest Physicians, 911 Busse Highway, Park Ridge,
Illinois 60068

Objectives: The objective of this project is to provide an educational opportunity for chest physicians to become proficient in the detection and management of asbestos-related pulmonary disease, including lung cancer. Chest physicians should be expected to serve as consultants to family practitioners for questions about asbestos-related pulmonary disease, yet this subject has not been emphasized in the training or continuing education programs for chest physicians in the past.

Accomplishments: A committee of experts was established, chaired by Dr. Robert Fontana of the Mayo Clinic. They have agreed on the material to be presented and have selected appropriate slides and tables. The slides include pictures of both X-rays and microscopic slides and are prepared in a special viewer for home use. These visual materials have been completed. Dr. Fontana is now editing the text of the accompanying syllabus, which will include appropriate tables on the epidemiology of asbestos-related disease.

Plans: It is expected that the self-teaching course materials will be available before August 1, together with plans for distribution, publicity and evaluation. Designed primarily for its members, the completed teaching set will also be provided to other physicians specializing in pulmonary disease and will be available for loan or purchase at cost from the ACCP to any health professional who wishes to use it.

Project Officer: Margaret H. Sloan, M.D.

Contract 95469: Cigarette Smoking in Teenage Females: A Social-Psychological-Behavioral Analysis and Further Evaluation of a Model Prevention Strategy

From 09/28/79 to 09/27/82

FY 81: \$92,650

Dr. Richard I. Evans, Department of Psychology, University of Houston, Central Campus, Houston, Texas 77004

Objectives: Since young females have been identified as a particularly high-risk group, the purpose of this project is to develop an effective strategy for preventing or delaying the onset of cigarette smoking in teenage females. The project is designed to: (1) identify, by means of a survey of seventh, ninth, and eleventh graders, those factors which appear to influence smoking initiation in young females; (2) incorporate information obtained from this survey into an intervention (i.e., smoking prevention) program suitable for seventh graders. Based on conceptualizations from the principal investigator's earlier research, Bandura's concepts of social learning and modeling and a behavioral variation of McGuire's cognitive inoculation model, this program employs an "inoculation-against-pressures-to-smoke" strategy; (3) implement and evaluate the intervention program in two local school districts.

Accomplishments: The first and second objectives listed above were accomplished during the first year of the project (10/79-09/80). The survey questionnaire and protocols for group and individual interviews were developed. Representative classes of seventh, ninth, and eleventh graders completed the questionnaire (n=558) and participated in the group interviews. Approximately 30 smokers and 30 nonsmokers (matched by gender and grade) were individually interviewed.

Analysis of these data provided information which was incorporated into three intervention films and into the intervention questionnaire. Major themes of the intervention films include the immediate physiological effects of cigarette smoking, and social influences to smoke and how to cope with these influences. Discussion guides for each film and posters depicting major messages contained in the films also were developed.

Work on the third objective--implementation and evaluation of the intervention program--began in October of 1980 and is continuing at the present time. Over 5,000 seventh grade students participated in the initial field entries. A similar number is expected to participate during April-May 1981.

Plans: Production of a "booster" film incorporating the major themes of the first three intervention films has begun. Filming will take place during the early summer, and the treatment groups will view this film during the eighth grade (October of 1981). Two field entries (measurements and interventions) are planned for October of 1981 and April of 1982.

Project Officer: Catherine S. Bell, M.S.

From 9/28/79 to 9/27/82

FY 81: 0(Annual \$157,000)

Dr. Richard Gams, University of Alabama, University Station, Birmingham,
Alabama 35294

Objectives: The purpose of the Communications Contract is to establish a Communications Office with up-to-date resources available to the lay public and health care professionals; develop material to educate target groups about cancer prevention, detection, treatment and rehabilitation; establish and operate a toll-free telephone cancer information service (CIS) to provide the public with current cancer-related information, and promote cancer education through county agents with the Auburn University County Extension Agencies in rural Alabama (Project HELP - Health Education Learning Program).

Accomplishments: The Alabama CIS opened April 1980 in two rural counties. By December 31, 1980, the CIS was available to all citizens of the state. The Resource Directory was completed and a person was hired half-time to handle publicity and promotion for the CIS and edit the CANCER COUNSELOR, a publication for Alabama physicians.

A slide/tape presentation which deals with the psychosocial problems and coping strategies of cancer patients and their families has been completed. Project HELP continued to expand its cancer education program targeted at Black women in Alabama; programming to encourage more of these women to obtain Pap tests and practice BSE was intensified, and data collection and evaluation plans were clarified. Publication of CANCER COUNSELOR was resumed, and the first issue will be mailed to Alabama physicians in April.

The Alabama CIS currently receives approximately 80 calls per week. Approximately 72% of Alabama CIS users are females, 15% are Black, and the majority of calls are cancer site specific. In rank order, breast, colo-rectal, and lung cancer are the three most common sites for which information is requested.

The first Alabama CIS User Survey found 24 callers out of 82 questionnaires returned from a random mailing of 100 made an appointment with a physician or clinic as a result of calling the CIS. An additional 20 talked via telephone to a physician or nurse about their problem.

Plans: Maintenance of the CIS, including consistent promotion and publicity activities and recruitment, training and supervision of the volunteers will continue. Project HELP will be expanded through continual training of community leaders who will conduct programs. Project HELP will be evaluated. Specific education problems have been uncovered by Project HELP staff, and these will be addressed during the remainder of the contract.

Project Officer: Thomas Kean

Contract 95472: Develop Course on Prevention, Focusing on Cancer for Medical Students and Residents

From 9/28/79 to 9/27/82

FY 81: \$82,700

Dr. Arthur Kohrman, Michigan State University, College of Human Medicine,
East Lansing, Michigan 48824

Objectives: It has been estimated that up to 80 percent of human neoplasms are directly related to environmental factors. Therefore, the consistent use of primary preventive strategies to reduce or eliminate exposure to carcinogenic agents becomes an important strategem in combatting cancer. Equally important is the use of secondary prevention, since early detection of many cancers increases chances of successful treatment. This contract will produce a course of instruction for medical students and residents to teach the concepts and methods of preventive medicine in clinical settings, methods of applying these concepts to the prevention of cancer, strategies for dealing with individual patients and the community and methods of critically assessing the research literature on cancer prevention to keep skills updated.

Accomplishments: During the period October 1, 1980 and September 30, 1981, project staff completed the initial development of the modules, media and evaluation instruments for a course on Cancer Prevention. The content for the modules was validated by means of a national needs assessment. A pilot version of the course was given April-June 1981. Using student/resident performance data, attitudinal data, module, and course evaluation data, the pilot version of the course was thoroughly analyzed. Currently, the course development team is reviewing the data and proposing possible revisions.

Plans: After the necessary revisions are completed, a revised version of this course will again be offered to M.D. and D.O. medical students at Michigan State University. The revised course will be offered during Spring Term 1982. Again, complete evaluation data will be collected, and the results will be documented. The course will then be packaged for replication by other schools.

Project Officer: Arlene R. Barro, Ph.D.

Contract 95474: Develop Course on Prevention, Focusing on Cancer for
Medical Students

From 9/28/79 to 9/27/82

FY 81: \$328,000

Dr. Richard E. Gallagher, Wayne State University School of Medicine, 540 East
Canfield Avenue, Detroit, Michigan 48201

Objectives: The course will seek to develop in the student a positive attitude about the efficacy of cancer prevention with emphasis on the skills necessary for this task. This course will, first of all, provide scientific background in carcinogenesis that will serve as a basis for the formulation, evaluation and management of cancer prevention protocols. Then, it will provide an understanding of the mechanisms by which human populations acquire cancer and the epidemiological methods of evaluation studies in carcinogenesis and cancer prevention. Finally, it will provide an approach whereby the student will learn the rudiments of the application of prevention measures in primary and community settings. The course will consist of 16 units or modules of instruction. Although this course is being designed for a medical student population, it may be of interest and have relevance to other professionals in health care settings.

Accomplishments: A curriculum committee composed of persons from diverse medical, behavioral and educational disciplines was formed. The major accomplishment of this committee was the formulation of the structure of the curriculum for the Cancer Prevention Course. The content of this curriculum was put in a topical outline format and revised by members of Wayne State University Medical School's Cancer Education Committee and selected people from the National Cancer Institute. Finally, based upon a revised content outline, behavioral objectives were developed.

To facilitate the implementation and evaluation of the course, time for the course content was obtained within the existing medical school curriculum. Production teams were formed and all but one module (XII) were produced. The formats include: slide/sound (microfiche), print, videotape and lecture/discussion. Selected modules are designed to use more than one format.

The module titles are as follows:

Developing Attitudes and Techniques

- I. Health Hazard Appraisal
- V. Physician/Patient Relationship: Implications for Prevention
- XIII. Keeping Current
- XV. Prevention Strategies

Carcinogenesis and Its Relationship to Cancer Prevention

II. Molecular Biology of Carcinogenesis:

- Part 1. Cell Transformation
- Part 2. Viral Carcinogenesis

Project Officer: Arlene R. Barro, Ph.D.

- III. Chemical and Physical Carcinogenesis
- IV. Part 1. Entry and Fate of Carcinogens in the Body
Part 2. Cell Kinetics

Epidemiological Aspects of Cancer Prevention

- VI. Data Observation
- VII. Part 1. Data Characterization
Part 2. Hypothesis Formation
- VIII. Evaluation of Data

Prevention at the Primary Care and Community Level

- IX. Risk Assessment Through Patient Interview
- X. Screening: Theory
- XI. Risk Assessment Through the Physical Examination
- XII. Risk Assessment: Application
- XV. The Community as a Resource for Personal Prevention Services
- XVI. Lifetime Health Maintenance Plan

As of March 31, 1981, all but two (XII and XIII) of the prototype modules will have undergone one "round" of field-testing (formative evaluation).

Plans: From April 1, 1981 to the completion of the production phase of the project (September 1982), the remaining module (XII) will be produced and field-tested. The other modules will be revised based on the results of Round I of field-testing. A longitudinal two-year post-course evaluation follow up is planned to assess the effect of the course on practice behavior. The course will be packaged for replication by other schools.

Contract 95475: Develop Course on Prevention, Focusing on Cancer for
Medical Students

From 9/28/79 to 9/27/82

FY 81: \$55,100

Dr. Frank Schimpfhauser, SUNY Buffalo School of Medicine, 3435 Main Street,
Buffalo, New York 14214

Objectives: Using the expertise of an interdisciplinary group of health professionals, the objective is to develop and test elective courses in prevention focusing on cancer for freshman and junior medical students. Historically, medical care and medical education have been oriented to diagnosis and treatment. The mission of this project is to improve the clinical practice of preventive oncology by producing physicians knowledgeable about and alert to the means for cancer control based on current knowledge in a variety of disciplines. A corollary objective is to develop the course in a format which can be replicated by other medical schools and updated as new knowledge is acquired.

Accomplishments: Course developers consisting of professionals from fields such as epidemiology, biostatistics, occupational medicine, pharmacology, surgery, nutrition, oncology, etc. have prepared detailed outlines of topics to be covered in the course. Student learning objectives have been delineated and refined. The content, student behavioral objectives and learning materials, and methods are being tested to ensure consistency with the following overall course theme: "The role and potential impact of the physician in disease prevention and the potential for the patient in controlling his own health status."

A library of resource materials has been developed and is constantly updated. It provides material specifically on cancer prevention topics, is used by the course developers and will be used by the prospective students.

A directory of field experiences is being compiled for evaluation as possible learning activities. Field experiences will be designed around specific unit objectives and areas of student interest.

Assessment will be in terms of student knowledge, skills, and attitudes acquired as a result of the course through written, oral, or demonstration methods.

Plans: Faculty and student guides specifying topics, objectives, resources, and expected performance levels have been developed. The courses are currently being field tested, and will be revised over the next year. The course will be packaged for replication by other schools.

Project Officer: Arlene R. Barro, Ph.D.

Contract 95476: Develop Course on Prevention, Focusing on Cancer for Medical Students and Residents

From 9/28/79 to 9/27/82

FY 81: \$185,200

Dr. Benjamin Trump, University of Maryland School of Medicine,
Baltimore, Maryland 21201

Objectives: The program is conceived to develop a course for medical students and residents on cancer prevention. Goals of this course will include:

1. Understand biology of human cancer.
2. Utilize concepts and techniques of epidemiology and preventive medicine to apply to cancer control in individuals and communities.

Accomplishments: The need for a multidisciplinary team approach was basic to the conceptualization of the course; participating departments and personnel have been identified in the Departments of Pathology, Epidemiology and Preventive Medicine, Family Medicine, and the Office of Medical Education. Content, process, and media for the course have been developed for 20 modules. Some focus on organ systems and some focus on principles of prevention. Objectives for the 20 modules have been reviewed by review committees, both in-house and at outside institutions. Media developed for each module may include videotapes, slide/tape shows, audio tapes, workbooks, self-instruction modules, references and reading lists, quizzes, evaluation, patient education kits, course content outlines, etc. The entire course was pilot tested in January 1981. Evaluation instruments were used to collect extensive data regarding the effectiveness of the teaching modalities. Of considerable importance to the development of this program is that the content of such a course must also be identified and developed.

Plans: Data collected at the time of the Pilot Course are being collated and analyzed. Based on preliminary data, it is anticipated that the following revisions will be required:

1. Consolidate objectives
2. Reduce redundancy among modules
3. Revise several modules extensively
4. Limit required reading
5. Refine existing media
6. Identify or develop additional media
7. Consolidate small group discussion topics
8. Reduce number of items on pre- and post-tests

The course will be packaged for replication by other schools.

Project Officer: Arlene R. Barro, Ph.D.

Contract 95477: Develop Course on Prevention, Focusing on Cancer for
Medical Students

From 9/28/79 to 9/27/82

FY 81: \$102,400

Dr. Ralph Ingersoll, Baylor College of Medicine, 1200 Morsund Avenue
Houston, Texas 77030

Objectives: To develop, implement, and evaluate a course in cancer prevention for undergraduate medical students and residents. The course is being developed by an interdisciplinary team of health professionals at Baylor College of Medicine and M.D. Anderson Cancer Center. The curriculum is being developed in a self-instructional format which can be replicated by other medical schools.

Accomplishments: Preparations were made during the first three quarters of this year to develop the pilot course which was offered June 23 - August 7, 1980. A review of the existing medical curriculum was conducted to determine where cancer information is taught. A review of relevant literature, books and resources was also conducted. Support was obtained from both the Texas Medical Center Library and M.D. Anderson Library in compiling course materials, A-V resources and reserve collections. An external review committee was appointed to serve as an outside evaluation team. An interdisciplinary faculty committee was appointed to develop the course. An in-depth interview was conducted with each member of the committee to determine course content and method. Committee members submitted names of visiting professors who would contribute to course sessions. Individual committee members were designated to plan and coordinate the 20 course sessions. Staff members worked with the faculty to develop course outlines and student outcomes. These designated student outcomes were developed into terminal behavioral objectives in the cognitive, affective, and psychomotor domains. Based on these objectives, evaluation measures were developed including attitudinal measures, pre and post tests to evaluate course effectiveness, and self-assessment exercises for each course session. Modules were developed for the pilot course. Each module contained written instructional objectives, case studies, a bibliography of learning resources, selected learning resources themselves, and self-evaluation and tutorial exercises. A student curriculum committee, consisting of a representative from each of the medical school classes, was appointed to assist in the development of the courses. Promotional material was sent to all Baylor students to acquaint them with the upcoming course. During the piloting of the course, selected sessions were recorded in order to analyze student discussions, comments and questions provoked by the case studies and session content. Students and faculty participants were asked to evaluate the pilot course. Based on these critiques and the evaluation of student achievement and attitudes, the course and its materials will be revised.

Plans: Learning materials and testing procedures will be evaluated, revised and updated. Additional case studies and tutorial exercises will be developed. The course will be offered to new groups of students. An instructional program for residents will be developed, conducted and evaluated. The course will be packaged for replication by other schools.

Project Officer: Arlene R. Barro, Ph.D.

Contract 95478: Approaches to Cancer Patient Management: A Synopsis
of the Networks (Breast)

From 09/28/79 to 06/30/81 FY 81: 0 (Ann. \$242,000)
Dr. Rosalie Kane and Dr. Robert Kane, The Rand Corporation, 1700 Main
Street, Santa Monica, California 90406

Objectives: The objective of this project is to prepare a monograph describing and generalizing from the work of 10 demonstration projects in breast cancer control funded by the NCI. These projects developed "breast cancer networks" with a mission to improve the management of breast cancer patients within a geographic area. The rationale for the project is based on the importance of determining what lessons can be learned from this initiative and extrapolating to future site-specific cancer control activities. Educational materials and strategies developed by the network are also to be analyzed.

Accomplishments: This project is nearing completion. The monograph, now in draft form, is expected to be available in the summer of 1981. As of April 1981, the Rand Corporation's multidisciplinary research team has accomplished the following:

1. Developed a framework for examining the organizational structures, data collection efforts, public education, professional education, and guidelines for care of all the breast cancer networks, thus permitting comparisons.
2. Made two site visits to each network, one concentrating on members of the central network group and one concentrating on affiliated or participating organizations.
3. Sponsored, planned, and conducted a two-day workshop during which participants from each of the networks interacted with Rand researchers to address some specific questions about the potential and limitations of the breast cancer networks and circumstances under which various strategies seem effective.
4. Drafted position papers on a number of theoretical issues related to breast cancer networks.
5. Telephoned 231 individuals from participating network hospitals that were not visited to gain additional perspectives on network roles and activities.
6. Assembled and annotated the educational materials derived from the networks.
7. Drafted the monograph, The Breast Cancer Networks: Organizing to Improve Management of a Disease, which, in turn, has been reviewed by NCI, network participants, and independent technical reviewers.

Project Officer: Rosemary Yancik, Ph.D.

Contract 95479: Develop Course on Prevention, Focusing on Cancer for
Physician Assistants

From 9/28/79 to 9/27/82

FY 81: \$110,300

Dr. Robert E. Roush, Center for Allied Health Professions, Baylor College
of Medicine, 1200 Morsund Avenue, Houston, Texas 77030

Objectives: The objective of this contract is to develop a course on prevention focusing on cancer prevention for students in the Physician Assistant Program at Baylor College of Medicine. Using the expertise of an interdisciplinary group of health professionals, the course will be developed over a three-year period and involve three interrelated phases: course development (year one), course implementation (year two), and course evaluation (year three).

Accomplishments: The primary accomplishment of the second year of the contract will have been the pilot testing of the cancer prevention course for physician assistants. The course will be offered to both first and second year PA students (N = 55) in an effort to establish baseline data on the efficacy of the instructional effort. A variety of assessments will be made to determine the extent to which students master the instructional objectives that were established during the initial year of the contract and the overall results of the completed instructional program.

Plans: The course will be pilot tested between the months of April and June 1981. Information on all aspects of the course will be gathered by project staff and provide a foundation from which revisions and adjustments can be made. The course will then be assembled into the format required by the contractor and field tested during the third and final year of the contract. The course will be packaged for replication by other schools.

Project Officer: Arlene R. Barro, Ph.D.

Contract 95480: Development of a Model Fellowship Program in Oncology Nursing Education

From 9/28/79 to 9/27/83

FY 81: \$278,000

Ms. Dorothy Siegele, San Jose State University, 125 South 7th, San Jose, California 95192

Objectives: A major objective of this project is to help resolve the nationwide shortage of qualified oncology nurse clinicians by providing advanced academic preparation to nurse educators who will develop and upgrade oncology programs at the graduate, undergraduate, and continuing education levels. Secondly, the model graduate curriculum developed by San Jose State University Department of Nursing and the University of Alabama School of Nursing - Birmingham can be shared with other institutions. Eleven U.S. schools offer graduate programs in cancer nursing, therefore, many nurse educators do not have the knowledge and clinical expertise necessary to develop and implement the oncology nursing education curricula needed to improve health care for cancer patients.

Accomplishments: A survey questionnaire documenting schools of nursing and health care agencies which could potentially provide fellows for the post-master's program was conducted. Fellow selection criteria were developed and nationwide publicity conducted primarily via mailed brochures and advertisement in professional journals. One group of fellows was admitted September 1980 and another group will attend the 1981-82 program. The staffs at the two universities involved in this project collaborated with each other and with the NCI staff and consultants to reach consensus concerning the philosophy, conceptual framework, and program objectives for the model curriculum. The year-long sequenced course of instruction was approved by appropriate university bodies at San Jose State University (SJSU) and by members of the advisory committee. Consortium relationships have been maintained with Stanford University Hospital/Clinics and affiliations established with several hospitals, community health agencies, and educational institutions for clinical and educational experiences. Key project personnel serve as faculty, and qualified clinical preceptors have been appointed as clinical associate professors. Course evaluation strategies have been identified and are consistent with the process and outcome evaluation plans being used and/or developed.

Plans: Plans for process and outcome evaluation will continue to be developed and implemented as the two groups of fellows complete the post-master's program. Two site visits will provide significant data to assess the strengths and limitations of the model curriculum and to make recommendations concerning its use and continuance.

Project Officer: Janet L. Lunceford, R.N., M.S.N.

Contract 95481: Develop Course on Prevention, Focusing on Cancer for
Medical Students

From 9/28/79 to 9/27/82

FY 81: \$79,800

Dr. Jerome B. Block, Harbor-UCLA Medical Center, Department of Medicine, 1000
Carson Street, Torrance, California 90509

Objectives: Under this contract the University of California at Los Angeles, School of Medicine, will develop a course on prevention focusing on cancer prevention. The course was developed by students under faculty supervision and directed to first and second-year medical students.

Accomplishments: The initial Pilot Course has been pilot tested in preparation for the formal, complete, effort in the Fall of 1981. A syllabus, instructional modules, criteria-referenced questions, and various attitudinal, demographic and evaluative testing instruments have been developed. Several video-taped "case histories in cancer prevention" have been developed as instructional aids.

Plans: The Pilot Course will be evaluated, modified after appropriate peer and faculty review, and formally presented in the Fall of 1981. The course will be packaged for replication by other schools.

Project Officer: Arlene R. Barro, Ph.D.

Contract 95482: Develop Course on Prevention, Focusing on Cancer for
Physician Assistants

From 9/28/79 to 9/27/82

FY 81: \$78,800

Dr. J. Dennis Hoban, Wake Forest University, Bowman Gray School of Medicine,
Winston-Salem, North Carolina 21703

Objectives: Bowman Gray School of Medicine undertook this project to increase the knowledge and skills requisite for its Physician Assistant graduates to practice preventive oncology. The integration of Bowman Gray's concern for prevention with its concern with cancer seemed appropriate and doable. The self-instructional, tutorial curriculum of the Physician Assistant Program and the medical educators and instructional designers of the Office of Educational Research and Services provided the framework and the educational resources to develop such a course on preventive oncology.

Accomplishments: During the first year of the project (October 1, 1979 to September 30, 1980), goals and objectives for a course in preventive oncology were developed, sequenced, and prioritized by a multi-disciplinary task force of medical specialists and instructional experts. During the first half of the project's second year (October 1980 - March 1981), those course goals and objectives guided the initial drafting of four self-instructional units by three interdisciplinary teams. Those four units were pilot tested by 14 second-year Physician Assistant students (February 9, 1981 - March 15, 1981). The results of that pilot test are presently governing the revision of the four units and the writing of an additional unit. In addition, three video-cassette programs are being produced, the total course is being formatted, test items are being constructed and Minimum Pass Levels established, student and faculty guides are being written, and finally, a course evaluation is being developed.

Plans: Our plans are to complete the total instructional package for NCI's critique (June 19, 1981), to field test the course (September 8-18, 1981), to make final revisions (September 1981 - April 1982) and throughout to document the development of the course (October 1979 - September 1982). The course will be packaged for replication by other schools.

Project Officer: Arlene R. Barro, Ph.D.

Contract 95483: Develop Course on Prevention, Focusing on Cancer for Nurse Practitioners and Physician Assistants

From 9/28/79 to 9/27/82

FY 81: \$96,500

Dr. Andrew Penman, MEDEX Northwest Physician Assistant Training Program,
University of Washington, 802 Coachhouse, 2309 N.E. 48th, Seattle,
Washington 98105

Objectives: The project utilizes a multidisciplinary group of health professionals to develop an elective course in cancer prevention for physician assistants and nurse practitioners. The course will be taught twice to 80 students and be revised as necessary. Extensive use of educational technology and evaluation will be made. During the fourth and fifth years the effect of the course will be field tested on students who took it vs. a control group.

Accomplishments: During the first 18 months, the project has developed an extensive course composed of three modules and 16 units on cancer prevention and early detection. Each unit contains detailed educational objectives, content outlines, plans for learning activities, references, and plans for evaluation. The syllabus is being reviewed by an advisory panel of cancer physicians and practicing physician assistants and nurse practitioners. Banks of test questions have been prepared.

A multidisciplinary course committee composed of nurses, health educators, physicians, epidemiologists, biostatisticians, and educators has been meeting regularly to review progress.

Plans: The course will be given in the spring quarter of 1981 and 1982, with revisions as indicated. Field research on its effects will take place in 1982-84. The course will be packaged for replication by other schools.

Project Officer: Arlene R. Barro, Ph.D.

Contract 95484: Develop Course on Prevention, Focusing on Cancer for
Nurse Practitioners

From 9/28/79 to 9/27/82 FY 81: \$99,500
Ms. Carol Reed-Ash, R.N., M.A., Memorial Sloan-Kettering Cancer Center,
1275 York Avenue, New York, New York 10021

Objectives: To develop a course in preventive health care, with a focus on cancer prevention, for nurse practitioners in community and occupational health settings. The goals of the course include improving nurse attitudes about cancer prevention and the expanding nursing role and increasing the range and frequency of nursing practice activities associated with cancer prevention. Additional goals include increasing nurse knowledge and skill in the area of cancer prevention. The project provides the opportunity to disseminate expert research and opinion about cancer prevention to nurses and, ultimately, to their clients and patients.

Accomplishments: The accomplishments of the project as of March 1, 1981 include (a) Two interdisciplinary committees of 20 top cancer experts and educational design experts have been formed and have functioned as a primary resource for course development. Physicians, nurses, and other health care professionals on the committees bring a broad range of expertise which contributes to a fully informed course in cancer prevention; (b) a complete review of cancer prevention literature has been performed; (c) a needs assessment survey has been conducted among 257 members of the target populations. This needs assessment provided us with valuable data which describes our target group as well as their perceptions of educational needs in the area of cancer prevention; (d) a full cancer prevention curriculum, in the form of 14 teaching/learning modules and an instructor manual has been completed. Prepared materials include module by module goals and objectives, module outlines, student workbooks (including exercises), supplementary reading lists, bibliographies, glossaries, lists of audio-visual aids, evaluation instruments, and guidelines for instructors such as appropriate feedback for exercises. Topics include content areas such as cancer concepts, clinical skills, teaching and counseling, research and data collection, and the role of the nurse in cancer prevention. Information is included from the fields of biology and medicine, nursing, sociology, psychology, economics, education, research, and management; (e) a full evaluation has been designed and instruments have been located and developed which measure participant change in the cognitive, affective, and psychomotor domains. Intervening variables that may affect the achievement of course goals will also be examined.

Plans: Plans for piloting, refining, and then field testing course materials and evaluation instruments are currently in progress. The course is being presented, as designed, to groups of nurse practitioners. A full evaluation of impact for each delivery and for impact over time is planned. Revisions and refinements, based on evaluation results, will be made. The course will be packaged for replication by other schools.

Project Officer: Arlene R. Barro, Ph.D.

Contract 95485: Professional Education in Cytology of Bladder, Lung,
Colorectal and Cervical Cancer

From 09/30/79 to 09/29/82 FY 81: 0 (Ann. \$74,000)
Dr. O. M. Blair, St. Louis University School of Medicine, 1402 S. Grand
Blvd., St. Louis, Missouri 63104

Objectives: The program is designed to provide specialized training to at least 250 cytotechnologists (CT) and 50 resident or Board-certified pathologists within the regional location of the program; Missouri, Kansas, Iowa, and Nebraska, with a maximum of 25-30 participants per course. The objectives are: to increase awareness of the importance of early diagnoses of pulmonary, colorectal, bladder, and cervical cancer; to update knowledge in current cytopreparatory methods, quality control, modern terminology and cytodiagnoses; and to contribute to the upgrading of cytopathological correlations and expertise.

Accomplishments: The first 18 months of this project have involved extensive design of the 2 week courses to be offered. Each course consists of 27 classroom hours and an equal number of laboratory demonstrations. The examinations and reviews have been structured for quality assurance in cytology. Enrollees were recruited primarily from Missouri, Kansas, Iowa, Nebraska, and from other neighboring states. The advertisement brochures and certificates of attendance have been designed and distributed as appropriate. The original teaching sets and the course manuals were completed on schedule, and are continually being updated.

The course has been accredited for 6.5 Continuing Education Units (CEU), for 65 credit hours in Continuing Medical Education (CME), and for 60 required (R) credit hours from the American Society of Cytology. The recruitment of guest faculty has been successful. Seventy-two participants were trained during the first five courses offered during 1979-80, with about 100 more expected in the second five by October 1981. New advertisement brochures for the 1981 courses are designed and distributed. The Steering Committee Meetings have effectively contributed to the overall planning and support of the program.

Plans: This project plan includes the giving of 6 more courses during 1981-82, in order to meet the goal of providing intensive specialized training to 300 participants during the 3 year period of the program, with continued availability of the training beyond that, probably using tuition charges.

Project Officer: Chauncey G. Bly, M.D., Ph.D.

Contract 95486: Pain Control in Cancer (Boston)

From 09/28/79 to 09/27/82

FY 81: 0 (Ann. \$151,000)

Dr. Paul Black, University Hospital Inc., 75 East Newton Street, Boston,
Massachusetts 02118

Objectives: Boston University is one of seven institutions participating in the collaborative study. A multidisciplinary team approach has been reported to be highly effective in reducing chronic pain in patients with benign disease, which in turn has reduced medical costs for these patients and contributed to their rehabilitation. The objective of the project Pain Control in Cancer at Boston University Medical Center is to evaluate the relative effectiveness of a multidisciplinary team approach as compared with the conventional consultation approach to managing pain in patients with cancer. Additionally, treatment strategies for managing cancer pain will be evaluated along with psychological, social, and emotional factors influencing pain.

Accomplishments: In the first year 62 patients were entered into the study. The project continued to gain support and acceptance. During this time extensive contacts were made throughout the hospital in order to educate all services about multidisciplinary pain management as well as about the research project. Specifically, on surgical and oncology floors, conferences were held with residents, nurses, and social workers concerning the team approach to pain management. As needed, individual patient centered conferences have been held to coordinate the patient's treatment planning to integrate the pain management teams' recommendations with the primary care staff. Lectures on multidisciplinary treatment of pain have been given to residents at University Hospital, and to staff at regional oncology hospitals. It is anticipated that pain management will be included in the training of psychology trainees and interns, psychiatry residents, and medical students as part of the elective curriculum.

Our representatives to the Data Management Committee and Steering Committee have participated fully in the collaborative planning and direction of the study.

Plans: Plans call for continuing evaluation of the effectiveness of the Pain Management Team in treating cancer pain. It is estimated that 160 patients will participate in the three year study. Pain and activity measures will also be evaluated for sensitivity to change in patient's self report. Patient data will be coded and entered on tapes for submission to the central data management contractor.

Project Officer: Donald N. Buell, M.D.

Contract 95487: Pain Control in Cancer

From 09/28/79 to 09/27/82 FY 81: 0 (Ann. \$125,817)
Dr. Ronald J. Ignelzi, University of California Medical Center,
225 Dickinson Street, San Diego, California 92103

Objectives: The objective of this study is to determine whether or not a pain management team is more efficacious in the management of pain in cancer than the conventional methods of treatment where the oncologist either treats the patient's pain or chooses conventional referral patterns. There is data to suggest that such a team approach in the management of benign pain has been successful, but to date there has been no objective quantitative study to determine whether or not this is also true of pain of cancer. The significance of this work is that if indeed a pain management team proves to better benefit the cancer patient with pain than conventional referral patterns, it should lead to the development of such clinics and better service to the patients with such pain.

Accomplishments: Since our last report we have enrolled 68 patients in the study. Data has been gathered and is being analyzed. There has been one general contractors meeting and in the near future there will be two more to establish policy for the remainder of the study based on the contractors' experience thus far.

Plans: Our plans are to continue enrolling patients into the study as outlined under the contract provisions. At present we plan to consider all patients in our design and data gathering.

Publications:

Ignelzi, R.J., and Atkinson, J.H.: Pain and its modulation, part 1 afferent mechanisms. Neurosurgery 6 (No. 5): 557-583, 1980.

Ignelzi, R.J., and Atkinson, J.H.: Pain and its modulation, part 2 efferent mechanisms. Neurosurgery 6 (No. 5): 584-590, 1980.

Kremer, E., Atkinson, J. H., and Ignelzi, R.J.: Measurement of pain: Patient preference does not confound pain measurement. Pain 1981 (IN PRESS)

Kremer, E., Atkinson, J.H., and Ignelzi, R.J.: Pain measurement: The effective dimensional measure of the McGill Pain Questionnaire with a cancer pain population. Pain 1981 (IN PRESS)

Project Officer: Donald N. Buell, M.D.

Contract 95488: Pain Control in Cancer (Jefferson Medical College)

From 09/28/79 to 09/27/82 FY 81: 0 (Ann. \$163,000)
Dr. Clorinda Margolis, Jefferson Medical College, 1025 Walnut Street
Philadelphia, Pennsylvania 19107

Objectives: Moderate to severe pain often accompanies the later stages of cancer and some patients experience intractable pain and suffering in the last month of their lives. This project hypothesizes that a multidisciplinary pain management team can treat women with pain for gynecological cancer more effectively than physicians who depend upon conventional means of pain control. This contract is part of a seven institution collaborative study.

Accomplishments: The Jefferson group has had a major role in developing the final study design and test instrument package format and serves the protocol chairman's function receiving patient entry and off study data. As an individual center, forty patients were entered into study. The Pain Management Team has been actively functioning and its composition has been revised to more adequately represent the patterns of intervention being recommended.

Clorinda G. Margolis, Ph.D., presented a workshop entitled "Hypnosis and Pain" at the Fourth Annual Conference and Workshops on Psychosomatic Disorders: New Trends in Pain Management at Thomas Jefferson University Hospital, March 1981. She has also made several presentations over the past year including two workshops entitled "Hypnosis for the Control of Pain and Crises Intervention" and "Use of Hypnotic Imagery with Cancer Patients" at the Society for Clinical and Experimental Hypnosis' 32nd Annual Workshops in October 1980; as well as a workshop at the Annual American Psychiatric Association Convention in May 1981 entitled "Chronic Benign Pain: Who Benefits."

Barbara B. Domangue, Ph.D., presented a paper entitled "Assessment Techniques in Chronic Pain" at the Fourth Annual Conference and Workshops on Psychosomatic Disorders: New Trends in Pain Management at Thomas Jefferson University Hospital, March 1980.

Plans: Currently we are involved in formalizing the plans for analysis of the data. We have recently:

- a. participated in the final revision of the data instrument package;
- b. participated in the development of the coding manual;
- c. begun to work on specific hypotheses to be tested by statistical analyses;
- d. begun work on preliminary analyses to ascertain broad differences between E and C groups.

We have participated in meetings of the Steering Committee and the Data Management Committee across sites.

Project Officer: Donald N. Buell, M.D.

From 09/28/79 to 09/27/82

FY 81: 0 (Ann. \$112,000)

Dr. John T. Bonica, University of Washington, Seattle, Washington 98195

Objectives: Uncontrolled pain is a major cause of suffering associated with the experience of cancer. Present evidence suggests that pain control carried out by a multidisciplinary team of specialists can control the suffering of the cancer patient more efficaciously than standard oncology pain management procedures; this, however, has not been documented by data obtained from a controlled study. The purpose of this project is to compare pain and pain related indices of invalidity in cancer patients managed by a multidisciplinary pain therapy team with similar measures in a group of patients receiving standard oncology pain therapy.

Accomplishments: We have been working in conjunction with six other centers engaged in the same project. The centers have arrived at a consensus regarding procedures for interview and data collection as well as test instruments. Our study involves comparisons of pain team managed cancer patients at the University of Washington's University Hospital with a similar population of control patients from Virginia Mason Medical Center. We have established research teams in both centers who are working in close relationship with their respective cancer services. The University of Washington team is also working closely with the clinical Pain Service. At present we are in the process of identifying, contacting, and interviewing patients in order to achieve our data collection goals. We are continuously developing and refining test instruments and interview procedures that help clarify the treatment needs and objectives for cancer pain patients. Beginning on October 1, 1980 the Virginia Mason Medical Center established its own pain therapy team and began to collect additional data on pain team managed patients in addition to control data. These members include physicians from the following fields: Radiation-Oncology, Medical-Oncology, Surgical-Oncology, Anesthesiology, and Rehabilitation Medicine. Also included are a Chaplin, registered pharmacist, and a registered nurse. Since its beginning date the Virginia Mason pain team has worked up a total of 15 patients. Patient accrual for the main thrust of the study has been as follows: University of Washington has started 28 and completed 15 patients. The Virginia Mason Medical Center has started 60 control patients and completed 51 of them. The University of Washington is currently following 14 patients, Virginia Mason 8. Completed patient figures include patients on whom some data was collected, but who were lost to the study due to disenrollment or death. Since data collection is currently in progress, final outcomes are not as yet available.

Plans: Data collection at University Hospital and Virginia Mason Medical Center will continue until the last six months of the project when work will begin on data reduction and analysis. Our colleagues at Battelle Research Institute will continue their work on data compilation and analysis, and they will take a major role in process and outcome evaluation as the project continues to develop.

Project Officer: Donald N. Buell, M.D.

Contract 95490: Pain Control in Cancer (Montefiore)

From 09/28/79 to 09/27/82

FY 81: 0 (Ann. \$126,000)

Dr. Deryck Duncalf, Montefiore Hospital and Medical Center, 111 East 210 Street,
Bronx, New York 10467

Objectives: The main objective of this project is to institute a program of pain control and treatment which utilizes a team approach. Multiple pain treatment approaches and assessment and planning are geared to the needs of individual patients and based on consensus decisions by the group. At this institution, the pain management team consists of representatives from; Anesthesiology, Oncology, Psychology, Radiotherapy, and Nursing, as well as consultants from such disciplines as Neurosurgery and Physical Medicine. A second objective is to assess the effectiveness of this team approach relative to traditional pain management, i.e., management by the primary physician. The third objective is to collaborate with six other centers in data collection, pooling and analysis.

Accomplishments: Based on agreements reached with other collaborating centers we began the definitive phase of the study on February 15, 1980.

This has consisted of seeing and evaluating patients with cancer pain, selection of appropriate subjects and randomization into study and control groups.

All study group patients are discussed at weekly meetings of our pain management team where their subsequent treatment is agreed upon by a consensus. To facilitate their management, written case summaries are prepared in advance of these meetings. Minutes of the meetings, as well as other pertinent data are kept on file.

Date collection is in progress, and in all, we have accumulated data on 70 patients.

Plans: It is anticipated that data collection will continue at, at least, the present rate. Specific designs for reporting data analysis will be formulated in collaborative meetings.

Project Officer: Donald N. Buell, M.D.

From 09/28/79 to 09/27/82 FY 81: 0 (Ann. \$144,000)
Dr. Richard Schwettmann, University of Wisconsin, Center for Health Sciences,
Department of Anesthesiology B6/387 CSC, 600 Highland Avenue,
Madison Wisconsin 53792

Objectives: To compare the effectiveness of control of pain in cancer patients as instituted by a multidisciplinary Pain Management Team (PMT) with pain control achieved by more traditional (individually planned by the attending physician) pain management.

Accomplishments: Study has reached the 18 month point of the contract award. Patient entry began on March 10, 1980. To date 84 patients have been randomized on the study; 26 patients have completed the 4 month follow-up period of the study. The patient accrual is on schedule and cooperation by the various services for referrals to the study continues at a most satisfying rate.

Data entry is nearly current on all psychological data collected. Medical and pharmacologic data is presently being coded for entry. Eighteen months remain on the contract award, and present trends indicate the goal of 120 patients can be reached.

No documented study results are available as yet, but staff and patient response indicate strong support for the aims of the study. An additional study has been initiated to determine any trends in changing drug therapy being brought about by the approach of the study.

Plans: If patient entry continues at present rates, contract objectives will be reached. The Pain Management Team has undergone several personnel changes but continues to function well. Assessment of their interaction continues and is being evaluated along with other collaborating institutions. Weekly meetings continue for members of the Pain Management Team and Research Team to assess problems and discuss pertinent concerns.

Project Officer: Donald N. Buell, M.D.



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